TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 45
Steps taken after authorisation – summary Page 46
Summary of Product Characteristics Page 47
Product Information Leaflet Page 47
Labelling Page 47
Annexes Page 48
On 14th September 2010, the MHRA granted Ipsen Limited a licence for the medicinal product Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection (PL 34926/0013). This is a prescription-only medicine (POM) to treat both locally advanced prostate cancer (prostate cancer that has spread to the immediate prostate gland area) and metastatic prostate cancer (prostate cancer that has spread to other parts of the body).

Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection contains the active substance triptorelin, which is similar to a hormone called gonadotrophin releasing hormone (GnRH). It acts by lowering the levels of the male hormone testosterone in the body. This is a long-acting formulation, designed to deliver 22.5mg of triptorelin over a 6-month period.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection outweigh the risks, hence a Marketing Authorisation has been granted.
DECAPEPTYL SR 22.5MG POWDER AND SOLVENT FOR SUSPENSION FOR INJECTION
PL 34926/0013

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Non-clinical assessment Page 7
Clinical assessment (including statistical assessment) Page 8
Overall conclusions and risk benefit assessment Page 11
**INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the MHRA granted Ipsen Limited a marketing authorisation for the medicinal product Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection (PL 34926/0013) on 14th September 2010. This product contains the active substance triptorelin and is indicated for the treatment of patients with locally advanced, non-metastatic prostate cancer, as an alternative to surgical castration, and the treatment of metastatic prostate cancer.

The application was submitted under Article 8(3) of Directive 2001/83/EC, as amended, a full-dossier application for a known active substance.

Decapeptyl contains triptorelin, which is an agonist analogue of gonadorelin, a synthetic decapeptide form of hypothalamic gonadotrophin-releasing hormone with similar properties. It is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, as well as other indications.

Triptorelin acts as a potent inhibitor of gonadotrophin-releasing hormone secretion, and thereby reduces testosterone levels, leading to castration. After initial administration, there is a transient increase in the circulating levels of lutinising hormone, follicle-stimulating hormone and testosterone. Triptorelin has a prolonged half-life compared to gonadotrophin-releasing hormone, due to its increased resistance to enzymatic degradation. The prolonged exposure to triptorelin, however, does not maintain the initial rise in lutinising hormone and testosterone. There is a persistent decrease in the levels of lutinising hormone and testosterone on continuous administration of triptorelin, due to pituitary desensitisation.

This application was discussed at the MHRA’s Commission on Human Medicines on 8th December 2009 and 15th July 2010. All recommendations made by the Commission were discussed and adequately resolved.
UKPAR Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Triptorelin embonate
Chemical name: L-Pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolyl-glycinamide, pamoate salt
Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH₂, pamoate salt
(D-Trp )-LHRH, pamoate salt

Structure:

Molecular formula: C₆₄H₈₂N₁₈O₁₃ . C₂₃H₁₆O₆ (triptorelin embonate)
Relative molecular mass: 1699.9
Appearance: Yellowish powder, soluble in N,N-dimethylformamide and pyridine, and practically insoluble in water

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Acceptable certificates of analysis have been provided for all reference standards used.

Batch analysis data have been provided and comply with the proposed specification.

Specifications have been provided for all aspects of the container-closure system used to store the active substance. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated to support the proposed retest period.
DRUG PRODUCT

Other ingredients
Other ingredients consist of poly(d,l-lactide-co-glycolide), mannitol, carmelllose sodium, polysorbate 80 and water for injections. With the exception of poly(d,l-lactide-co-glycolide), all excipients comply with their respective European Pharmacopoeia monograph. Poly(d,l-lactide-co-glycolide) has been shown to comply with a suitable in-house specification.

Certificates of analysis have been provided for all excipients, showing compliance with the proposed specification.

None of the excipients are derived from materials of animal or human origin, or from a genetically modified source.

Product development
The objective of the pharmaceutical development programme was to produce a safe, efficacious product for injection, containing 22.5mg triptorelin (in the form of triptorelin pamoate).

Satisfactory product development data were submitted with this application.

Manufacture
A satisfactory batch formula has been provided for the manufacture of the product along with an appropriate account of the manufacturing process.

In-process controls are appropriate considering the nature of the product and the method of manufacture.

The manufacturing process has been validated and has shown satisfactory results.

Finished product specification
The finished product specifications proposed at both release and shelf-life are acceptable, and provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container-closure system
The container-closure system consists of a box, which contains:
- a 6ml vial with bromobutyl stopper and an aluminium flip-off cap (containing the powder product)
- a 2ml ampoule of sterile solvent for suspension
- a blister containing one injection syringe and two injection needles.

Suitable specifications and certificates of analysis have been provided for the finished packaging. All packaging components comply with relevant guidelines concerning contact with foodstuff.
Stability of the product
Stability data has been provided for batches of the finished product stored in-line with current guidelines. All batches were manufactured by the finished product manufacturer, according to the proposed manufacturing method and stored in the packaging proposed for marketing.

Based on these stability studies, a shelf-life of 3 years has been proposed, with storage conditions of “Do not store above 25°C. Keep the container in the outer carton. The reconstituted suspension for injection should be used immediately.” These are acceptable.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labels are pharmaceutically acceptable.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

Pharmaceutical expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

CONCLUSION
It is recommended that a Marketing Authorisation is granted for this product.
NON-CLINICAL ASSESSMENT

With the exception of one pharmacokinetic study, no new non-clinical data were submitted with this application. The pharmacodynamic, pharmacokinetic and toxicological properties of triptorelin pamoate are well-known, thus no new non-clinical data were required.

A pharmacokinetic study to assess the serum testosterone and triptorelin levels in rats was submitted with this application. The study was performed in-line with current Good Laboratory Practice (GLP).

Following the screening of 14 different microparticule formulations, formulation A, formulation B and formulation C were selected for further clinical evaluation in four distinct studies. The formulation selection was based on measured serum testosterone and triptorelin levels, following administration of all tested formulations. The three chosen formulations induced castration until at least 6 months (24 weeks). Serum triptorelin levels following administration of formulations A and B were >500 pg/ml until Month 6. The formulation C showed a slightly different profile, released much less triptorelin until 4 months (serum triptorelin levels > 300 pg/ml) and more between 4 and 6 months (> 800 pg/ml).

The three selected slow-release triptorelin formulations (A, B and C) were administered to rats as a single intramuscular injection, in order to compare testosterone pharmacodynamic profiles, as well as triptorelin pharmacokinetics. The mean profiles of serum testosterone levels after administration of formulations A and B were similar until Day 168 (24 weeks). Formulation C showed a slightly higher serum testosterone profile during the first 12 weeks following administration, however, the level did not go over 4 nmol/L. In the three treated groups, testosterone levels remained lower than non-treated animals at all timepoints. The individual triptorelin release profiles of the two formulations A and B were similar. A burst was observed within 1 day of administration, followed by a decrease up to Day 28 (4 weeks). Then, an increase of triptorelin leading to a plateau of 1,000 to 2,000 pg/ml was observed until Day 84 (12 weeks). Triptorelin decreased to 300-800 pg/ml at Day 168 (24 weeks). The triptorelin release was consistently in correlation with a low mean serum testosterone value. A modest increase in testosterone at the end of the study (Week 28) was correlated with a lower level of triptorelin.

Non-clinical 6 month-Formulation Batches Selected for further Clinical Evaluation (see Non-clinical Report DEB-TRI6M-006 M.4.2.2.7.2)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Batch number</th>
<th>Non-clinical study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>126A046M</td>
<td>DEB-TRI6M-004</td>
</tr>
<tr>
<td>B</td>
<td>126C065M</td>
<td>DEB-TRI6M-003</td>
</tr>
<tr>
<td>C</td>
<td>126C052</td>
<td>DEB-TRI6M-002</td>
</tr>
</tbody>
</table>

1 without microgranules of triptorelin pamoate 11.25 mg (triptorelin 3-month formulation)

Further studies performed in rats after administration of clinical formulation A batches #4126M0503 (clinical batch used in clinical study DEB-TRI6M-201 #4126M0605 (clinical batch used in the first injection of clinical study DEB-TRI6M-301) and
UKPAR Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

#4126M0606 (clinical batch used in the second injection of clinical study DEB-TRI6M-301) microgranule, confirmed previous data concerning serum testosterone and triptorelin release profiles. Following administration of the two test formulation batches #4126M0605 and #4126M0606, testosterone rapidly decreased to very low levels and remained approximately at a plateau (~2.2 nmol/l) until Day 168 (24 weeks). A slight testosterone increase up to 3.9 nmol/l was observed at Day 182 (26 weeks) for both formulation batches. A peak in serum triptorelin levels was measured within 1 day of administration for the three formulations, followed by a decrease up to Day 28 (4 weeks). Then, an increase of triptorelin levels, leading to a plateau of 1900 to 800 pg/ml, was observed until Day 140 (20 weeks). Triptorelin decreased to 300-350 pg/ml at Day 168 (24 weeks). The triptorelin release was consistently correlated with a low mean serum testosterone value. A modest increase in testosterone at the end of the study (Day 182, week 26) was correlated with a lower level of triptorelin.

Clinical Batches of Formulations A, B and C of the 6 Month-Formulations of Triptorelin investigated in the Pilot Phase 2 Study DEB-TRI6M-201 (RP-2469-F001 RP -2469-F004)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Batch number</th>
<th>Clinical study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4126M0503</td>
<td>DEB-TRI6M-201</td>
</tr>
<tr>
<td>B</td>
<td>4126M0501</td>
<td>DEB-TRI6M-201</td>
</tr>
<tr>
<td>C</td>
<td>4126M0502</td>
<td>DEB-TRI6M-201</td>
</tr>
</tbody>
</table>

The non-clinical data of the batch # 4126M0503 are reported in the study report RP-2469-F001 RP-2469-F004. For the Batch # 4126M0501, only serum testosterone levels had been measured (data not reported). The Batch # 4126M0502 had not been tested in rat.

Based on the results of the Phase II study, formulation A was selected for further clinical evaluation in a Phase III study (DEB-TRI6M-301).

Clinical Batches of Formulation A investigated in the Phase 3 study DEB-TRI6M-301) (see report RP-2469-F001 RP-2469-F004 in M.4.2.2.7.3)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Batch number</th>
<th>Clinical study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4126M0605</td>
<td>DEB-TRI6M-301</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1st injection)</td>
</tr>
<tr>
<td>A</td>
<td>4126M0606</td>
<td>DEB-TRI6M-301</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2nd injection)</td>
</tr>
</tbody>
</table>

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

The SPC, PIL and labels are acceptable from a non-clinical viewpoint.

A suitable justification for the lack of an environmental risk assessment has been submitted, in-line with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/447/00). It is anticipated that marketing the
UKPAR Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

proposed products will not result in an overall increase in environmental exposure to triptorelin.

It is recommended that a Marketing Authorisation is granted for this product.
CLINICAL ASSESSMENT

1 CLINICAL PHARMACOLOGY
1.1 PHARMACOKINETICS
1.1.1 Introduction and overview
The pivotal study, DEB-TRI6M-301 was conducted as a multicentre, open, non-comparative, phase III study on the efficacy, pharmacokinetics and safety of two injections of Triptorelin Embonate 22.5 mg 6-month formulation in patients with advanced prostate cancer.

Triptorelin pharmacokinetics and the effects on testosterone pharmacodynamics were studied, in a 15-patient subset, from the 120 patients recruited into the pivotal study. The pharmacokinetic data obtained is compared with the pharmacokinetic data obtained from the clinical studies, E28 52014 701 comparing the Ipsen 1-month and 3-month formulations; and DEB-96-TRI-01 comparing the 1-month and 3-month Debiopharm formulations of triptorelin.

All 120 patients, recruited to the pivotal study, were to receive two consecutive injections of triptorelin embonate 22.5 mg on Day 1 and Day 169 by intramuscular (I.M) injection

Blood samples for triptorelin assessments were taken at 0 hours (prior to injection), 1, 2, 3, 4, 6, 8 and 12 hours after injection on study Day 1, and then on Days 2, 3, 5, 8, 15, 29, 57, 85, 113, 141. Blood samples were collected again on Day 169 at 0h (prior to injection) at 1, 2, 3, 4, 6, 8 and 12 hours after injection, and then on Days 170, 171, 173, 176, 183, 197, 225, 253, 281, 309 and 337. Triptorelin levels were measured in a central laboratory in The Netherlands (Xendo Laboratories). The determinations of triptorelin in human serum were performed using two validated different radioimmunoassay (Debiopharm/Xendo studies n° DEB-TRIO-021/VS417 and RP-2469-F008/VS0657).

The applicant states that the first assay was not sensitive enough (LOQ: 500 pg/mL), and therefore a new assay was validated (LOQ: 150 pg/mL) and that was used in the latest phase of the Bioanalytical Study. All samples having concentrations below 500 pg/mL in the initial phase of the Bioanalytical Study were also repeated with the adjusted assay. The applicant states that as the two methods were successfully compared as similar, their simultaneous use within one study was allowed.

The observations with regards to triptorelin pharmacokinetics are as below

Results
Triptorelin levels
Triptorelin descriptive statistics at each time point are presented in the tables below.
UKPAR Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

Table 14.3-11. (part 1 of 4) Triptorelin Concentrations by Time Point

| Table 14.3-11. (part 2 of 4) Triptorelin Concentrations by Time Point |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| N | DAY1-H0 | DAY1-H1 | DAY1-H2 | DAY1-H3 | DAY1-H4 | DAY1-H5 | DAY1-H6 | DAY1-H7 | DAY1-H8 | DAY1-H9 | DAY1-H10 |
| Mean (SD) | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| SEM | 0.03 | 0.18 | 0.18 | 0.02 | 0.03 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| CV | 3.00 | 1.86 | 1.86 | 2.50 | 2.50 | 2.50 | 2.50 | 2.50 | 2.50 | 2.50 | 2.50 |
| Median | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 | 12.00 |
| Min - Max | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 |
| 95% CI (Lower CI; Upper CI) | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 | 9.00 - 12.00 |

The figure below presents the same variables on a log 10 scale.
The serum concentrations of triptorelin in the above tables show identical patterns after the two injections, with a peak in the triptorelin concentrations 3 hours after the injection, followed by an initial rapid decrease, then a slower rate of decrease, and then an almost steady serum concentration of triptorelin. This is graphically represented in the figure above.

**Triptorelin pharmacokinetic metrics**
Two patients (01602 and 05612) discontinued the study after Day 176 and Day 197; therefore, the AUC$_{169-337}$d was not calculated for these patients. Descriptive statistics of triptorelin pharmacokinetic metrics for the first injection (AUC$_{1-169}$d, C$_{max}$$_{1-169}$d, t$_{max}$$_{1-169}$d), the second injection (AUC$_{169-337}$d, C$_{max}$$_{169-337}$d, t$_{max}$$_{169-337}$d) and the pre-dose concentration (C$_{0h}$) are summarized in the table below:

<table>
<thead>
<tr>
<th>Statistic</th>
<th>First injection</th>
<th></th>
<th>Second injection</th>
<th></th>
<th></th>
<th>C$<em>{dist}$$</em>{max}$ [ng/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC [days* ng/mL]</td>
<td>C$_{max}$ [ng/mL]</td>
<td>t$_{max}$ [h]</td>
<td>AUC [days* ng/mL]</td>
<td>C$_{max}$ [ng/mL]</td>
<td>t$_{max}$ [h]</td>
</tr>
<tr>
<td>N</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>103.71</td>
<td>40.04</td>
<td>-</td>
<td>111.50</td>
<td>36.31</td>
<td>-</td>
</tr>
<tr>
<td>90% CI of geometric mean</td>
<td>(86.62; 124.17)</td>
<td>(32.53; 49.14)</td>
<td>-</td>
<td>(97.90; 126.99)</td>
<td>(30.61; 43.07)</td>
<td>-</td>
</tr>
<tr>
<td>Median</td>
<td>-</td>
<td>-</td>
<td>3.00</td>
<td>-</td>
<td>-</td>
<td>4.00</td>
</tr>
<tr>
<td>90% non-parametric CI of median</td>
<td>-</td>
<td>-</td>
<td>(2; 12)</td>
<td>-</td>
<td>-</td>
<td>(3; 8)</td>
</tr>
</tbody>
</table>

The AUC and C$_{max}$ accumulation ratio (second administration over first administration) and the non-parametric Hahn and Meeker 90% CI for the t$_{max}$ median difference post second administration minus first administration are summarized in the table below:

<table>
<thead>
<tr>
<th>N</th>
<th>AUC</th>
<th>C$_{max}$</th>
<th>t$_{max}$ [h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean</td>
<td>13</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>90% CI of geometric mean</td>
<td>(0.98; 1.24)</td>
<td>(0.72; 1.14)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**Summary of the Pharmacokinetic Results**
In summary, the results of the pivotal study DEB-TRI6M-301 show a mean (geometric) C$_{max}$ value of 40.0 ng/ml observed at a median t$_{max}$ of 3 (range 2-12) hours, for the 6-month formulation triptorelin 22.5 mg after the first injection. A geometric mean of C$_{max}$ of 36.31 ng/ml, was observed at median t$_{max}$ of 4 hours after the second injection. These results, and the results from studies involving the 1- and 3-month Ipsen formulations (triptorelin acetate; study E28 52014 701), and the 1- and 3-month Debiopharm formulations (triptorelin pamoate; study DEB-96-TRI-01), are listed in the tables below.
Both the Debiopharm formulations and the 6-month formulation have the geometric mean (and range) of C\(_{\text{max}}\) quoted. The C\(_{\text{max}}\) values of 40 (22.2-76.8) ng/ml and 36.31 (30.61-43.07) ng/ml for the 6-month triptorelin formulation is most comparable to the C\(_{\text{max}}\) of 35.8 (16.5-57.4) ng/ml quoted for the 3-month Debiopharm formulation. The applicant explains that this is expected, since the comparable microgranules contained in the Debiopharm 3-month formulation, provide the initial release burst of triptorelin in both the 3- and 6-month formulations. The geometric mean AUC over 6 months for the 6-month formulation was lower, when compared to the geometric mean AUC’s for the 1-month and 3-month Debiopharm formulations (103.7 days*ng/ml vs. 197.9 days*ng/ml and 202.3 days*ng/ml, respectively).

The C\(_{\text{max}}\) for the 1-month Debiopharm formulation was lower (15.6 ng/ml), and the applicant justifies this as expected due to the lower triptorelin content.

The study with Ipsen 3-month and 1-month formulations have the mean C\(_{\text{max}}\) quoted. The C\(_{\text{max}}\) for the 3-month formulation was 0.931 ng/ml (+/- 0.375), and 0.812 ng/ml (+/- 0.489) for the 1-month formulation, at median t\(_{\text{max}}\) of 7 and 2 days, respectively.

The geometric mean AUC over 6 months for the 6-month formulation is about half that for the 1- and 3-month formulations (112 vs. 202 and 198 days*ng/ml for the 6-month, 3-month, and 1-month formulations, respectively).
The principal evaluation criteria was pharmacodynamic equivalence, based on the percentage of patients who had a plasma testosterone level < 1.73 nmol/l (50 ng/dL) on Day 84. This study was not a pharmacokinetic equivalence study and the sampling times did not cover the first hours of the triptorelin release. The relatively large difference in $T_{\text{max}}$ for serum triptorelin levels noted between the results with the 6-month formulation from the pivotal study (median $T_{\text{max}}$ 3 hours) and the results of the study E 52014 701 with 1-month (median $T_{\text{max}}$ 2 days) and 3-month (median $T_{\text{max}}$ 7 days) formulations could be explained by the differences in the first pharmacokinetic sampling times between the two studies. In Study E28 52014 701, the first pharmacokinetic sampling was on Day 2 whereas, in the pivotal 6-month formulation study, the earliest pharmacokinetic samples were taken at 1, 2, 3, 4, 6, 8 and 12 hours on Day 1. Due to this difference in sampling times, the comparison of $T_{\text{max}}$ results from these two clinical studies is not meaningful. In addition, the differences in the early pharmacokinetic parameters between the 1- and 3-month formulations, and the new 6-month formulations, could be explained by the differences in delivery forms, which are not exactly the same. These differences in microparticles (microspheres for the 1- and 3-month Ipsen formulations, microgranules for the 6-month formulation) probably have an impact on the respective triptorelin release profiles ($T_{\text{max}}$, $C_{\text{max}}$, AUC), however, they do not necessarily have any significant impact on the testosterone pharmacodynamics.

In response to a question concerning the comparability of results between the pivotal study and Study E28 52014 701, the applicant again refers to the differences in sampling times between studies. It is further discussed that the treatment objective was to obtain the agreed pharmacodynamic effect, i.e. serum testosterone levels below 1.735 nmol/l. Despite the differences in the triptorelin pharmacokinetic profiles observed between the 3- and 6-month formulations, after achievement of castration, the mean testosterone levels are maintained well-below the castration threshold with both formulations due to the desensitisation of the pituitary, which is maintained with very low levels of triptorelin. The results for the pharmacodynamic effects are seen to be similar between the studies, in spite of differences noted in the pharmacokinetic parameters. Therefore, any pharmacokinetic differences are unlikely to affect the pharmacodynamic effects or efficacy.

The applicant discusses that triptorelin pharmacokinetics is not a reliable surrogate marker for the assessment of bioequivalence of triptorelin formulations, since the pharmacokinetic/pharmacodynamic (PK/PD) relationship of triptorelin is highly non-linear and time-dependent. The lower geometric mean AUC for the 6-month formulation is to a great extent explained by a single initial release burst for the 6-month formulation compared with 2 for the 3-month formulation and 6 for the 1-month formulation ($C_{\text{max}}$ of 40.0, 35.8 and 15.6 ng/mL for 6-, 3- and 1-month formulations, respectively). The applicant justifies that this is not clinically relevant, since the triptorelin bursts during the maintenance phase of treatment do not contribute to a pharmacodynamic response due to the pituitary desensitisation at the time of the repeated triptorelin injections.

**Clinical Assessor’s Comments:**
The applicant has discussed and justified the reasons for difference in $t_{\text{max}}$ between the different formulations - median 3 hours (range 2-12) for the 6-
month formulation, in comparison to 7 days and 2 days for the 3-month and 1-month formulations, respectively.

The results for the testosterone pharmacodynamic effects are seen to be similar between the studies, in spite of differences noted in the pharmacokinetic parameters (see below). Therefore, any pharmacokinetic differences are unlikely to affect the (testosterone) pharmacodynamic effects or efficacy.

The geometric mean AUC for the 6-month formulation is lower, in comparison to the 1- and 3-month Debiopharm formulations. This may not be clinically significant, since the testosterone pharmacodynamic response with pituitary desensitisation is maintained with low levels of triptorelin, after the initial desensitisation. This concept is true with other gonadotrophin-releasing hormone analogues as well. The applicant’s discussion regarding this is acceptable.

1.1.2 Absorption
As shown in the pivotal study, following intramuscular injection of the Decapeptyl SR 22.5mg formulation, in prostate cancer patients, a mean (geometric) $C_{\text{max}}$ of 40 (22.2-76.8) ng/ml was reached at a median $t_{\text{max}}$ of 3 (2-12) hours.

The absorption of the 6-month formulation is most comparable with the pharmacokinetic parameters of the 3-month Debiopharm formulation of triptorelin (pamoate/ embonate). This has been justified by the applicant due the comparable microgranules present in both the formulations, which provide the initial burst in triptorelin levels.

1.1.3 Distribution
No new data have been submitted.

Gonadotrophin-releasing hormone and its agonists are not bound to circulating serum proteins. Triptorelin is not active when given orally. The study by Fuller et al (BJCP 1997; 44:335-341) regarding the pharmacokinetics of triptorelin after intravenous administration in healthy individuals, and individuals with renal and hepatic impairment, describes the distribution and elimination according to the three-compartment model, with elimination half-lives of 6 minutes, 45 minutes and 3 hours.

1.1.4 Drug Interactions:
The applicant reports no known drug-drug interactions with triptorelin, and states that there have been no reported interactions over more than 20 years of marketing experience.

Clinical Assessor’s Comments:
There have been no drug interaction studies conducted and in the absence of data it is advisable to avoid hyperprolactinemic drugs concomitantly with triptorelin, since hyperprolactinaemia reduces the number of pituitary gonadotrophin-releasing hormone receptors.

The following statement has been added to section 4.5 of the Decapeptyl
SmPC: “Drugs which raise prolactin levels should not be prescribed concomitantly as they reduce the level of GnRH receptors in the pituitary.”

1.1.5 Metabolism
No new data have been submitted.

Clinical Assessor's Comments:
Gonadotrophin-releasing hormone is rapidly degraded by peptidases in several organ tissues, such as the liver, kidneys, anterior and posterior pituitary, hypothalamus and brain tissue. Triptorelin is a synthetic decapeptide agonist analogue of gonadotrophin-releasing hormone, and is more resistant to enzymatic degradation due to modification of the amino acid at position six.

Like other peptides, the metabolism of triptorelin involves degradation to smaller peptide fragments and individual amino acids, and unlikely to involve hepatic microsomal enzymes. Pharmacokinetic data suggest the C-terminal fragments produced by tissue degradation are either completely degraded in the tissues, or rapidly degraded in plasma, or cleared by the kidneys.

1.1.6 Excretion
No new data have been submitted.

Clinical Assessor's Comments:
Both renal and hepatic functions are important in the clearance of triptorelin. The study by Fuller et al suggests that the liver plays a predominant role in subjects suffering from some degree of renal impairment.

1.1.7 Intra- and inter-individual variability
No new data have been submitted.

1.1.8 Special pharmacokinetic considerations in target population
Decapeptyl SR 22.5 mg is intended for use in advanced and metastatic prostate cancer. The studies submitted in support of this application have been conducted in this target population.

Clinical Assessor's Comments:
These patients can commonly have some degree of renal impairment. The study by Fuller et al (BJCP 1997; 44: 335-341) demonstrated that the total clearance of triptorelin decreased with increasing renal impairment, and was even lower in patients with hepatic insufficiency. It should be noted that the healthy individuals included in this study had a high creatinine clearance, which was twice as high as the intended target population of older patients suffering from prostate cancer in which a safe and effective dose of triptorelin has been determined. Furthermore, the prolonged half-lives have no practical significance since the drug is administered as a slow-release formulation whose release rate is much slower than the elimination of the drug. Hence, there are no dose modifications described in these conditions.
1.1.9 Special populations
Decapeptyl SR 22.5 mg is intended for use in advanced metastatic prostate cancer. It is not intended for use in women and children.

For exploratory reasons, a subgroups analysis of the achievement of castration by ethnic origin, body mass index (BMI) and age category was performed. The results and tables are presented and discussed in the Section “Efficacy Results”.

1.1.10 Assessor’s overall conclusions on pharmacokinetics
The pharmacokinetic parameters of the 6-month formulation Decapeptyl SR 22.5mg were studied in a 15-patient subset in the pivotal study DEB-TRI6M-301. The data obtained have been compared with the results for the 1-month and 3-month Debiopharm formulations (triptorelin embonate) from the study DEB-96-TRI-01. The geometric mean $C_{\text{max}}$ values of 40mg/ml (after the first injection) and 36.31 ng/ml (after the second injection) obtained for the 6-month formulation is most comparable to the 3-month Debiopharm formulation, with a geometric mean $C_{\text{max}}$ of 35.8 ng/ml. These two products contain comparable microgranules responsible for the initial burst in triptorelin levels after administration.

The geometric mean AUC over 6 months for the 6-month formulation was lower in comparison to the other formulations (103.7 days*ng/ml vs. 202.3 for the 3-month, and 197.9 days*ng/ml for the 1-month Debiopharm formulations). This may not be of clinical significance, since castration is maintained with low levels of triptorelin after the initial pituitary desensitisation has occurred. This has been suitably discussed by the applicant and has been justified as not being clinically relevant as the triptorelin bursts during the maintenance phase of treatment do not contribute to a pharmacodynamic response due to the pituitary desensitisation at the time of the repeated triptorelin injections.

Despite the differences in the triptorelin pharmacokinetic profiles observed between the 3- and 6-month formulations, after achievement of castration, the mean testosterone levels are maintained well-below the castration threshold with both formulations due to the desensitisation of the pituitary, which is maintained with very low levels of triptorelin. The results for the pharmacodynamic effects are seen to be similar between the studies, in spite of differences noted in the pharmacokinetic parameters. Therefore, any pharmacokinetic differences are unlikely to affect the pharmacodynamic effects or efficacy.

There are no new data with regards to the distribution, metabolism, excretion, and individual variability. This is acceptable.

1.2 PHARMACODYNAMICS
1.2.1 Introduction
Assessment of testosterone pharmacodynamics of triptorelin embonate 22.5 mg 6-month formulation was one of the secondary objectives of the pivotal study DEB-TRI6M-301. This was assessed in the same 15 patients’ subset, as described above, in whom the assessment of triptorelin pharmacokinetics was conducted.
Testosterone levels were measured at 0 hours (prior to injection) on Day 1 and on Days 2, 3, 5, 8, 15, 22, 29, 57, 85, 113, 141, 169 (prior to injection), 170, 171, 197, 225, 253, 281, 309 and 337. If testosterone levels were > 1.735nmol/l on Day 171, they were to be repeated on Days 173 and 176 (if applicable) and then followed up at an interval of 48-72 hours until castration levels were reached again or for a maximum of 2 weeks post dosing. The testosterone pharmacodynamic parameters from the pivotal study (DEB-TRI6M-301) with the 6-month formulation were compared with results from studies with the 1- and 3-month Ipsen formulations (study E28 52014 701) and the 1- and 3-month Debiopharm formulations (study DEB-96-TRI-01).

The effect of the triptorelin embonate 22.5 mg on the lutinising hormone level was studied as one of the secondary objectives, in all the patients. This is discussed below.

### 1.2.2 Primary Pharmacodynamics and mechanism of action

Triptorelin is a potent inhibitor of gonadotrophin secretion when given continuously and in therapeutic doses. There is a transient rise in the circulating levels of lutinising hormone, follicle-stimulating hormone and testosterone. After chronic and continuous administration there is a sustained decrease in the lutinising hormone and follicle-stimulating hormone levels. This then results in a decreased testicular and ovarian steroidogenesis.

The lutinising hormone levels were measured during the study, as part of the secondary objective of the study- to assess the absence of gonadotrophin (lutinising hormone) stimulation 2 hours after the first and second injection of triptorelin embonate 22.5mg 6-month formulation. The results are discussed below.

### 1.2.3 Secondary Pharmacodynamics

Testosterone pharmacodynamic parameters were assessed in a 15-patient subset in the pivotal study to assess the pharmacodynamic actions of triptorelin. These parameters are summarised in the table below and compared with similar data available from the studies with the 1-month and 3-month Ipsen and Debiopharm formulations.

<table>
<thead>
<tr>
<th>Formulation [study]</th>
<th>N</th>
<th>Geometric Mean (range) $C_{max}$ after 1st injection (nmol/mL)</th>
<th>Median (range) $t_{max}$ after 1st injection (day)</th>
<th>Geometric mean Time to castration (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month [DEB-TRI6M-301 pivotal study]</td>
<td>15</td>
<td>22.8 (14.1-49.2)</td>
<td>5 (2.5)</td>
<td>18.8 (12.8-24.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Formulation</th>
<th>N</th>
<th>Mean (range) $C_{max}$ after 1st injection (nmol/mL)</th>
<th>Mean (range) $t_{max}$ after 1st injection (day)</th>
<th>Mean (range) Time to castration (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-month</td>
<td>36</td>
<td>25.8 (13.6-47.8)</td>
<td>2.4 (2.7)</td>
<td>19.3 (13.7-32.1)</td>
</tr>
<tr>
<td>1-month</td>
<td>34</td>
<td>23.7 (12.4-41.2)</td>
<td>2.1 (2.7)</td>
<td>18.4 (11.8-32.2)</td>
</tr>
</tbody>
</table>
All the formulations show comparable mean C_max and t_max for testosterone, following the first injection.

### Clinical Assessor’s Comments:

The wide variations between the pharmacokinetic parameters (C_max and AUC) for triptorelin between the different formulations has been discussed and justified. These are not thought to affect the pharmacodynamics.

However, the C_max and the t_max for testosterone levels after administration of the 6-month formulation of triptorelin are comparable to the 1- and 3-month Ipsen and Debiopharm formulations.

The time to castration is also comparable to the data from the studies with the 1- and 3-month Ipsen formulations. These data are not available with the Debiopharm formulation from the DEB-96-TRI-01 study.

The serum testosterone concentrations by time points are described in the tables below:
The number of patients in the Intention-To-Treat (ITT) and Per-Protocol (PP) populations varies depending on the days. The pharmacokinetic subset demonstrates a rise in the mean serum testosterone after the first injection followed by a subsequent fall in the serum levels. This rise in mean serum testosterone levels is not seen with the second injection (after Day 169). The mean +/- standard deviation serum testosterone levels for the ITT and PP populations are displayed in the figures below.

The figure for PK subset population (15 patients) is presented below.
The effect of pituitary desensitisation observed with triptorelin 22.5 mg in the pivotal study is described in the figure below. There was a rise in lutinising hormone levels immediately after the 1st injection of triptorelin, which was followed by suppression in the lutinising level. After the 2nd injection, the extent of the rise and subsequent suppression was much lower, demonstrating adequate pituitary desensitisation at the time of the 2nd injection of triptorelin 22.5 mg at Day 169.

After the 1st injection, there was a rise in the mean lutinising hormone levels from 7.9 IU/l (range: 1.2-47.0) at the baseline to 38.3 IU/l (range 11.0-145.7) at 2 hours. At the 2nd injection, the mean lutinising hormone was suppressed to only 0.14 IU/l (range: 0.1-4.6) due to the desensitisation of the pituitary gonadotrophin-releasing hormone receptors, and 2 hours after the 2nd injection the mean lutinising hormone level had increased to 0.32 IU/L (range: 0-15.2).

1.2.4 Pharmacodynamics of active metabolites
Not applicable.
1.2.5 Pharmacokinetic – pharmacodynamic relationship

It appears that once achieved, desensitisation of the pituitary is maintained at very low levels of triptorelin.

**Clinical Assessor's Comments:**

As previously noted, the initial triptorelin exposures ($C_{max}$) varied between the different triptorelin formulations (1- and 3-month Ipsen formulations, 1- and 3-month Debiopharm formulations, and the 6-month formulations). Despite this, the testosterone $C_{max}$ was comparable for all the formulations.

In the clinical overview, the applicant discusses that once the desensitisation of the pituitary occurred and castration was induced, the down-regulation of gonadotrophin-releasing hormone receptors and castration was maintained with very low systemic levels of triptorelin.

Pituitary desensitisation is well-demonstrated by the results obtained for the secondary objective- assessment of the absence of gonadotrophin (lutinising hormone) stimulation 2 hours after the first and second injection of triptorelin embonate 22.5 mg 6-month formulation. The results show a negligible rise in lutinising hormone levels following the second injection of triptorelin, as compared to the rise in serum levels after the first injection (discussed in detail above in Section 2.2.5).

The results obtained by the assessment of testosterone pharmacodynamics of triptorelin (presented in the tables above on serum testosterone levels by timepoint) show a rise in testosterone levels after the 1st triptorelin injection, but no rise in serum testosterone levels after the 2nd injection.

1.2.6 Pharmacodynamic interactions

No data submitted.

1.2.7 Intra- and inter-individual variability in pharmacodynamic response

(Including genetic differences)

No new data submitted.

1.2.8 Assessor’s overall conclusions on pharmacodynamics

The pharmacodynamic action of triptorelin on testosterone is an accepted; surrogate parameter for determining efficacy of gonadotrophin-releasing hormone agonists and the castration level was defined according to the internationally accepted cut-off level of testosterone serum levels $\leq 1.735$ nmol/l ($\leq 50$ ng/dl).

From the results obtained from the assessment of lutinising hormone stimulation 2 hours after the first and second injection, the pattern of changes in the lutinising hormone levels is as would be expected following administration of a gonadotrophin-releasing hormone analogue. The first injection is followed by a surge in the serum lutinising hormone level, as expected. The measurement prior to the second injection show that the serum levels are well below the pre-triptorelin levels. The levels taken 2 hours after the second injection shows that there is only a minimal surge in lutinising hormone levels (from mean 0.14 to 0.32 IU/L). This indicates that the desensitisation of the pituitary that occurs after the
first injection is maintained at the time of the second injection at Day 169, i.e., for the entire expected duration of treatment with one injection.

This effect is also supported by the pattern observed with measurement of testosterone levels in the 15-patient subset. These results show a rise in the testosterone levels following the first injection. This is then subsequently followed by a fall in the testosterone levels. The second injection of triptorelin does not cause a further rise in the testosterone levels.

2 CLINICAL EFICACY
2.1 INTRODUCTION
The applicant has submitted the results of the pivotal Phase III study DEB-TRI6M-301, in support of this application. The formulation of triptorelin pamoate used in the pivotal study was decided on the basis of the results obtained from the Phase II comparative study, DEB-TRI6M-201, conducted with three formulations of triptorelin pamoate 22.5 mg 6-month injections.

The results of the pivotal study have been compared with the results of studies with the 1-month and 3-month formulations of triptorelin, to show similarity of the 6-month formulation to these formulations in terms of the efficacy, pharmacokinetics, pharmacodynamics and safety.

2.2 DOSE-RESPONSE STUDIES
Study DEB-TRI6M-201 evaluated three different formulations of triptorelin embonate 22.5 mg, one of which (arm A) was identical to the formulation selected for further clinical development. A total of 24 patients with histologically or cytologically proven advanced prostate cancer (stages T3-NxMx or T1N1-3Mx or T1N2M1) or with rising prostate specific androgens after failing local therapy were given a single intramuscular injection of one of three formulations of triptorelin embonate 22.5mg. The primary efficacy endpoints were the proportion of patients achieving castrate levels of testosterone (≤1.735nmol/l) at Day 29 and the proportion of patients maintaining castration levels from Day 57 to 169.

Blood samples for testosterone assessments were drawn prior to study drug injection on Day 1 and on Days 2, 3, 4, 8, 15, 29, 57, 85, 113, 141 and 169. All 8 patients who received the formulation used for further clinical development achieved castrate levels of testosterone on Day 29 and maintained castrate levels from Days 57-169.

The other two formulations studied were rejected for the following reasons:
• One formulation did not maintain castration in all eight patients until Day 169.
• One formulation was rejected since its manufacturing method was different from the one for the approved 1- and 3-month formulations.

2.3 MAIN STUDY
The main study submitted in support of this application is:
• DEB-TRI6M-301- pivotal phase III study.
2.3.1 Study Design (Pivotal study- DEB-TRI6M-301)
A multi-centre, open, non-comparative, Phase III study to assess the efficacy, pharmacokinetics and safety of two injections of triptorelin 22.5mg 6-month formulation in patients with advanced prostate cancer.

Objectives
Primary objective
The primary objective of this study was to evaluate the efficacy of triptorelin embonate 22.5mg 6-month formulation in achieving castration levels of testosterone ($\leq 1.735$nmol/L) on Day 29 (i.e. 28 days after study drug injection) and in maintaining castration levels of serum testosterone from Month 2 to end of Month 12 (Week 48) in patients with advanced prostate cancer.

Secondary objectives
The secondary objectives were:

- In all patients to assess the:
  - absence of gonadotropin (lutinising hormone) stimulation 2 hours after the first and second injection of triptorelin embonate 22.5mg 6-month formulation
  - efficacy of triptorelin embonate 22.5mg 6-month formulation by mean change in prostate specific antigen (PSA) levels from baseline throughout treatment
  - safety profile of triptorelin embonate 22.5 mg 6-month formulation.

- In a subset of 60 patients to assess the:
  - absence of testosterone increase above 1.735 nmol/L 48 hours after the second injection of triptorelin embonate 22.5 mg 6-month formulation (“acute-on-chronic” phenomenon).

- In a subset of 15 patients (pharmacokinetic/pharmcodynamic objectives) to assess the:
  - testosterone pharmacodynamics of triptorelin embonate 22.5mg 6-month formulation;
  - pharmacokinetics of triptorelin embonate 22.5mg 6-month formulation.

Clinical Assessor’s Comment:
The stated level of $\leq1.735$nmol/L is acceptable as the castration level of testosterone.

In a subset of 15 patients (pharmacokinetic/pharmcodynamic objectives) to assess the:

Study Population
Between 10th July 2006 and 4th September 2006, 120 patients with advanced prostate cancer were enrolled in 13 centres in the Republic of South Africa.

Study Treatments
The study was conducted as a multicentre, non-comparative Phase III study. One single triptorelin 6-month formulation was tested in all 120 patients. For all patients, the study duration was 337 days, and was to receive two consequent injections of triptorelin 22.5mg on Day 1 and Day 169 by intramuscular injection.

All patients received the first injection of triptorelin embonate on Day 1. One patient died on Day 85 and, therefore, did not receive the 2nd injection on Day 169.
Time window to evaluate adherence to the visit schedule was defined relative to Day 1 visit, as exact scheduled day for visits on Days 1, 2, 3, 5, 8, 169, 170, 171, 173 and 176, and as scheduled Day ± 1 day for visits on Days 15, 22, 29, 57, 85, 113, 141, 183, 197, 225, 253, 281, 309 and 337.

**Primary endpoints:**
1. Percentage of patients achieving castrate levels of serum testosterone (≤ 1.735 nmol/L) by Day 29
2. Percentage of patients maintaining castrate levels of serum testosterone (≤ 1.735 nmol/L) from Month 2 to end of Month 12 (Week 48).

**Secondary endpoints:**
1. The proportion of patients showing ≤ 1.0 IU/l increase in serum lutinising hormone from 0 to 2 hours after the first and second injection of study drug
2. Prostate specific antigen (PSA) change in percent from baseline throughout treatment
3. Percentage of patients, in a subset of 60 patients, who show testosterone levels >1.735 nmol/l 48 hours after the second injection
4. Testosterone pharmacodynamics in a subset of 15 patients: $\text{AUC}_{[1-169d]}$, $\text{C}_{\text{max}}$, $\text{T}_{\text{max}}$, $\text{T}_{\text{cast}}$
5. Triptorelin pharmacokinetic metrics in a subset of 15 patients (for both injection periods): $\text{AUC}_{[1-169d]}$, $\text{AUC}_{[169-337d]}$, $\text{C}_{\text{max}}[1-169d]$, $\text{C}_{\text{max}}[169-337d]$, $\text{T}_{\text{max}}[1-169d]$, $\text{T}_{\text{max}}[169-337d]$.

**Randomisation**
Not applicable

**Blinding**
Not applicable

---

**Clinical Assessor’s Comments on Study Design:**

*The chosen population for the study is acceptable and is representative of the population in whom Triptorelin SR 22.5 mg would be used.*

*The chosen primary and secondary endpoints are adequate. Testosterone pharmacodynamics are accepted surrogates for determining the efficacy of gonadotropin releasing hormone agonists.*

*The lutinising hormone increase of ≤1.0 IU/l was set as an index to assess the degree of pituitary desensitisation. As lutinising hormone is driving testosterone secretion, changes in testosterone concentrations have been shown to be highly correlated with changes in lutinising hormone concentrations, but with a time delay.*

*There is very little missing data, and the method by which missing data is handled is acceptable.*

*The study is a non-comparative study. The applicant has provided a rationale for conducting a non-comparative pivotal study. It has been uniformly accepted by both oncology and urology communities that the suppression of*
testosterone secretion is a relevant biological surrogate endpoint for the palliative treatment of advanced prostate cancer. The absence of a comparative study is justified by the use of this well-established and objective surrogate marker, serum testosterone, for the effective treatment of advanced prostate cancer. The applicant’s discussion regarding the comparison of the efficacy based on the surrogate endpoint, serum testosterone, can be accepted. The rates of achievement of castration in the present study are comparable to that obtained with the 1-month and 3-monthly preparations.

Data suggests an increased risk of diabetes and cardiovascular disease in men with prostate cancer on gonadotrophin releasing hormone agonists. This was the reason for this point to be raised at the first assessment. A search of the US Food and Drug Administration (FDA) website shows that an ongoing safety review of gonadotrophin releasing hormone agonists has been initiated, in view of this evidence. According to the FDA, the potential safety risk arose after several studies suggested a small statistically significant increase in the risk of diabetes and cardiovascular disease. However, the results are not yet conclusive.

The applicant states that despite the difference in duration of assessment periods, the 6-month formulation has a comparable safety profile to that of the 1-month and 3-month formulations. Furthermore, the applicant justifies that the adverse events with triptorelin are related to the pharmacological action of testosterone suppression; and testosterone suppression with the 6-month formulation has been shown to be identical between the 1-month and 3-month formulations.

### 2.3.2 Results

#### Patient disposition

<table>
<thead>
<tr>
<th>Safety</th>
<th>ITT</th>
<th>PP</th>
<th>Subset of 60</th>
<th>PK/PD subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>120</td>
<td>115</td>
<td>60</td>
<td>15</td>
</tr>
</tbody>
</table>

Out of the 120 patients enrolled, 115 (95.8%) completed the study. Three patients died, one was “lost to follow-up” and one patient withdrew consent. There were five major protocol violations and these patients were excluded from the per protocol (PP) population.

A subset, of 60 patients, was created to assess the “acute-on-chronic” phenomenon (increase in serum testosterone above castrate levels after the 2nd injection of triptorelin).

A pharmacokinetic/pharmacodynamic subset of 15 patients was created at three investigational sites among patients who agreed to frequent blood samplings.

The study, included patients with a rising prostate specific antigen, after failed local therapy, with no other evidence of disease progression. They included 28% of the
study population. Patients with metastatic disease at baseline comprised 8% of the study population.

**Baseline characteristics and co-variates**

The demographic characteristics of the study population are summarised in the table below:

<table>
<thead>
<tr>
<th>Age</th>
<th>Safety N=120</th>
<th>ITT N=120</th>
<th>PP N=115</th>
<th>PK Subset N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>120</td>
<td>120</td>
<td>115</td>
<td>15</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>71.11 (8.46)</td>
<td>71.11 (8.46)</td>
<td>71.28 (6.36)</td>
<td>58.46 (8.93)</td>
</tr>
<tr>
<td>SEM</td>
<td>0.77</td>
<td>0.77</td>
<td>0.78</td>
<td>2.31</td>
</tr>
<tr>
<td>CV</td>
<td>11.90</td>
<td>11.90</td>
<td>11.73</td>
<td>13.06</td>
</tr>
<tr>
<td>Median</td>
<td>69.09</td>
<td>69.09</td>
<td>69.95</td>
<td>68.59</td>
</tr>
<tr>
<td>Min - Max</td>
<td>50.75 - 92.74</td>
<td>50.75 - 92.74</td>
<td>50.75 - 92.74</td>
<td>54.20 - 81.22</td>
</tr>
<tr>
<td>95% (LowerCI; UpperCI)</td>
<td>(68.58; 72.64)</td>
<td>(69.58; 72.64)</td>
<td>(69.74; 72.82)</td>
<td>(63.45; 72.34)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Safety N=120</th>
<th>ITT N=120</th>
<th>PP N=115</th>
<th>PK Subset N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>119</td>
<td>119</td>
<td>114</td>
<td>15</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>83.46 (16.38)</td>
<td>83.46 (16.38)</td>
<td>83.68 (16.57)</td>
<td>82.83 (11.07)</td>
</tr>
<tr>
<td>SEM</td>
<td>1.50</td>
<td>1.50</td>
<td>1.55</td>
<td>2.86</td>
</tr>
<tr>
<td>CV</td>
<td>19.63</td>
<td>19.63</td>
<td>19.60</td>
<td>13.35</td>
</tr>
<tr>
<td>Median</td>
<td>51.00</td>
<td>51.00</td>
<td>51.00</td>
<td>80.00</td>
</tr>
<tr>
<td>Min - Max</td>
<td>46.50 - 136.20</td>
<td>46.50 - 136.20</td>
<td>46.50 - 136.20</td>
<td>55.00 - 98.00</td>
</tr>
<tr>
<td>95% (LowerCI; UpperCI)</td>
<td>(80.49; 85.44)</td>
<td>(80.49; 85.44)</td>
<td>(60.60; 86.75)</td>
<td>(76.70; 88.96)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Safety N=120</th>
<th>ITT N=120</th>
<th>PP N=115</th>
<th>PK Subset N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>110</td>
<td>120</td>
<td>115</td>
<td>15</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>173.38 (6.17)</td>
<td>173.38 (6.17)</td>
<td>173.47 (6.20)</td>
<td>174.40 (7.21)</td>
</tr>
<tr>
<td>SEM</td>
<td>0.75</td>
<td>0.75</td>
<td>0.76</td>
<td>1.86</td>
</tr>
<tr>
<td>CV</td>
<td>4.71</td>
<td>4.71</td>
<td>4.73</td>
<td>4.13</td>
</tr>
<tr>
<td>Median</td>
<td>173.50</td>
<td>173.50</td>
<td>174.00</td>
<td>175.00</td>
</tr>
<tr>
<td>Min - Max</td>
<td>150.00 - 192.00</td>
<td>150.00 - 192.00</td>
<td>150.00 - 192.00</td>
<td>161.00 - 186.00</td>
</tr>
<tr>
<td>95% (LowerCI; UpperCI)</td>
<td>(171.50; 174.05)</td>
<td>(171.50; 174.05)</td>
<td>(171.96; 174.96)</td>
<td>(170.45; 178.29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnic Origin</th>
<th>Safety N=120</th>
<th>ITT N=120</th>
<th>PP N=115</th>
<th>PK Subset N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Black</td>
<td>27 (22.59)%</td>
<td>27 (22.59)%</td>
<td>27 (23.48)%</td>
<td>5 (33.33)%</td>
</tr>
<tr>
<td>Colored (Mixed Race)</td>
<td>16 (13.33)%</td>
<td>16 (13.33)%</td>
<td>13 (11.30)%</td>
<td>5 (20.00)%</td>
</tr>
<tr>
<td>White</td>
<td>77 (64.17)%</td>
<td>77 (64.17)%</td>
<td>75 (65.22)%</td>
<td>7 (46.67)%</td>
</tr>
</tbody>
</table>

**Protocol deviations and violations**

Five major protocol violations occurred during the study. These are listed in the table below.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Violation</th>
</tr>
</thead>
<tbody>
<tr>
<td>05609</td>
<td>Concomitant antiandrogens (Androcur®) for 32 days started on Day 172</td>
</tr>
<tr>
<td>07602</td>
<td>Concomitant systemic glucocorticoids (Prednisone®) and anti-androgen (Casodex®) taken from Day 282 ongoing at study end</td>
</tr>
<tr>
<td>08609</td>
<td>Bilateral orchectomy on Day 317, 21 days prior to Day 337 visit</td>
</tr>
<tr>
<td>09607</td>
<td>Day 337 visit performed 28 days after schedule</td>
</tr>
<tr>
<td>10602</td>
<td>Concomitant systemic glucocorticoids (Prednisone®) taken from Day 305 mostly until end of study</td>
</tr>
</tbody>
</table>

There were several minor violations that have been listed in the clinical study report.

**Clinical Assessor’s Comments:**

All the patients entered were accounted for. Handling of missing data, protocol violations were satisfactory.

The reasons for the five drop-outs have been described as above, in the study report, and they are acceptable.

**Primary efficacy analysis** (based on primary endpoints)
The efficacy results from the pivotal study (DEB-TRI6M-301) are presented below. The comparison of the primary efficacy variables for the proposed product, with the results obtained with the 1-month and 3-month formulations are summarised in the table in Section 3.6, and discussed in Section 3.8. All the patients who received any dose (120) were analysed for safety. All patients enrolled (120) were included in the intention-to-treat (ITT) populations. The per-protocol (PP) population included all patients in the ITT population, except those with major protocol violation/deviation (n=115).

1. **Percentage of patients achieving castrate testosterone levels on Day 29**
The percentage of patients achieving castration levels of serum testosterone ($\leq 1.735$ nmol/L) at Day 29 is listed in presented in the table below.

<table>
<thead>
<tr>
<th></th>
<th>ITT (N=120)</th>
<th>PP (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>117 (97.50%)</td>
<td>112 (97.39%)</td>
</tr>
<tr>
<td>95% exact binomial CI</td>
<td>(92.87%; 99.48%)</td>
<td>(92.57%; 99.46%)</td>
</tr>
</tbody>
</table>

In the ITT population, three patients did not achieve castrate testosterone levels at Day 29. All the three patients remained on the study.

Subgroup analyses of the achievement of castration by ethnic origin, body mass index (BMI) and age categories were performed. The proportion of patients achieving castration levels of testosterone at Day 29, broken down by ethnic origin and by BMI, and age category, are presented in the table below. It is stated that there was no statistically significant difference between the ethnic origin, BMI or age categories in terms of the proportion of patients achieving castration at Day 29. The results are presented in the tables below.

a. **Proportion of Patients Maintaining Castration Levels (Principal Analysis) broken down by ethnic origin**

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American / Black N (%)</td>
<td>26 (96.30%)</td>
<td>13 (96.30%)</td>
</tr>
<tr>
<td>95% CI of Yes</td>
<td>(81.03%; 99.91%)</td>
<td>(81.03%; 99.91%)</td>
</tr>
<tr>
<td>No</td>
<td>1 (3.70%)</td>
<td>2 (3.70%)</td>
</tr>
<tr>
<td></td>
<td>(100.00%)</td>
<td>(100.00%)</td>
</tr>
<tr>
<td>Colored (Mixed Race) N (%)</td>
<td>16 (100.00%)</td>
<td>13 (100.00%)</td>
</tr>
<tr>
<td>95% CI of Yes</td>
<td>(79.41%; 100.00%)</td>
<td>(75.29%; 100.00%)</td>
</tr>
<tr>
<td>No</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td></td>
<td>(100.00%)</td>
<td>(100.00%)</td>
</tr>
<tr>
<td>White N (%)</td>
<td>75 (97.40%)</td>
<td>73 (97.33%)</td>
</tr>
<tr>
<td>95% CI of Yes</td>
<td>(90.93%; 99.68%)</td>
<td>(90.70%; 99.68%)</td>
</tr>
<tr>
<td>No</td>
<td>2 (2.60%)</td>
<td>2 (2.67%)</td>
</tr>
</tbody>
</table>

b. **Proportion of Patients Maintaining Castration Levels (Principal Analysis) broken down by BMI category**
c. Proportion of Patients Maintaining Castration Levels (Principal Analysis) broken down by age category

<table>
<thead>
<tr>
<th></th>
<th>&lt;70 Years N (%)</th>
<th>&gt;=70 Years N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT Maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>53 (92.59%)</td>
<td>54 (93.10%)</td>
</tr>
<tr>
<td>Failure</td>
<td>4 (7.41%)</td>
<td>4 (6.90%)</td>
</tr>
<tr>
<td>95%CI of Success</td>
<td>(83.27%; 96.09%)</td>
<td>(83.00%; 98.05%)</td>
</tr>
<tr>
<td>PP Maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>50 (92.59%)</td>
<td>52 (92.86%)</td>
</tr>
<tr>
<td>Failure</td>
<td>4 (7.41%)</td>
<td>4 (7.14%)</td>
</tr>
<tr>
<td>95%CI of Success</td>
<td>(82.11%; 97.94%)</td>
<td>(82.71%; 98.02%)</td>
</tr>
</tbody>
</table>

**Clinical Assessor's Comment:**

The failure rate in the group with BMI >25 was 8.86%, in comparison to a failure rate of 2.86% in the group with BMI <25, in the ITT population. The failure rates were 9.21% vs 3.03% for the BMI>25 and the BMI<25 groups respectively, in the PP population. The mean BMI of the study population was 27.7 kg/m² (18.7-40.9 kg/m²). In the discussion regarding efficacy in the study protocol, there is mention of three patients who were clearly clinical failures. One of these patients had a BMI of 40.2 kg/m², and was not castrated at any point after the 1st injection of triptorelin.

The exploratory subgroup analysis of data from the 6-month study to assess the potential impact of BMI on the achievement and maintenance of castration did not reveal any clinically significant differences between the groups (BMI ≥25 kg/m² and BMI <25 kg/m²).
In the ITT and PP populations, five drop-out patients discontinued the study due to non-drug-related reasons. Therefore, these patients were excluded from the analysis. In the remaining 115 patients, eight did not maintain castration.

**Sensitivity analysis: percentage of patients maintaining castration testosterone levels from Day 57 to Day 337 – survival analysis**

The percentage of patients maintaining castration levels from Day 57 to Day 337 was estimated using survival analysis techniques (Kaplan-Meyer product limit method). The analysis used the time to event, i.e. from Day 57 to the first timepoint showing a testosterone level above castration (>1.735 nmol/l). A patient with no such event was censored at the time of his last visit.

In this analysis, the non-drug-related drop-outs were treated as censored observations at the moment of study discontinuation. The product limit estimate results are summarized in the table below:

<table>
<thead>
<tr>
<th>Population</th>
<th>Product Limit Survival Estimate at Day 337</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (N = 120)</td>
<td>Maintenance rate</td>
</tr>
<tr>
<td></td>
<td>95% CI for the maintenance rate</td>
</tr>
<tr>
<td>PP (N = 115)</td>
<td>Maintenance rate</td>
</tr>
<tr>
<td></td>
<td>95% CI for the maintenance rate</td>
</tr>
</tbody>
</table>
Sensitivity analysis: percentage of patients maintaining castrate testosterone levels from Day 57 to Day 337 – worst case analysis

For this analysis, all patients having missing data at a certain visit were considered as failures. The percentage of patients maintaining castration levels from Day 57 to Day 337 according this analysis are summarized in the table below.

<table>
<thead>
<tr>
<th></th>
<th>ITT (N analysis = 120)</th>
<th>PP (N analysis = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>98 (81.67%)</td>
<td>94 (81.74%)</td>
</tr>
<tr>
<td>95% exact binomial CI</td>
<td>(73.57% ; 88.14%)</td>
<td>(73.45% ; 88.33%)</td>
</tr>
</tbody>
</table>

Secondary efficacy analyses (based on secondary endpoints)

1. Proportion of patients showing ≤ 1.0 IU/L increase in serum lutinising hormone

The proportion of patients showing ≤ 1.0 IU/L increase in serum lutinising hormone from 0 to 2 hours after the first and second injection of study drug is summarized in the table below:

<table>
<thead>
<tr>
<th>Day</th>
<th>ITT</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td></td>
<td>(0.00% ; 3.03%)</td>
<td>(0.00% ; 3.18%)</td>
</tr>
<tr>
<td>169</td>
<td>117 (98.32%)</td>
<td>112 (98.25%)</td>
</tr>
<tr>
<td></td>
<td>(94.06% ; 99.80%)</td>
<td>(93.81% ; 99.79%)</td>
</tr>
</tbody>
</table>

On Day 1 after the first injection, no patient showed ≤ 1.0 IU/L increase in serum lutinising hormone from 0 to 2 hours. On Day 169, after the second injection about 98.3% of patients in both ITT and PP populations showed ≤ 1.0 IU/L increase in serum lutinising hormone. On Day 169, two patients who were never castrated after the first injection had an increase in serum lutinising hormone from 0 to 2 hours of 1.1 IU/L and 15.2 IU/L, respectively. One patient, discontinued the study before Day 169 due to fatal myocardial infarction.
2. Percentage changes in PSA from Day 1 throughout treatment
Detailed descriptive statistics on percentage decreases in prostate specific antigen for ITT and PP populations are summarized in the table below:

<table>
<thead>
<tr>
<th>ITT</th>
<th>Percentage change from Baseline to Day 85</th>
<th>Percentage change from Baseline to Day 169</th>
<th>Percentage change from Baseline to Day 253</th>
<th>Percentage change from Baseline to Day 337</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>-89.34 (17.59)</td>
<td>-90.20 (21.58)</td>
<td>-90.07 (20.73)</td>
<td>-82.31 (66.71)</td>
</tr>
<tr>
<td>PP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>-89.28 (17.84)</td>
<td>-89.94 (21.92)</td>
<td>-89.90 (21.07)</td>
<td>-82.18 (67.85)</td>
</tr>
</tbody>
</table>

In addition, the percentage of patients with normal prostate specific antigen values (i.e. <4µg/L) on Day 337 was analyzed. The results are summarized below:

<table>
<thead>
<tr>
<th>Normalized PSA</th>
<th>ITT (%)</th>
<th>PP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>93 (80.87)%</td>
<td>91 (82.73)%</td>
</tr>
</tbody>
</table>

3. Proportion of patients not castrated on Day 171 and beyond (subset of 60 patients)
The “acute-on-chronic” phenomenon was studied in a subset of 60 patients. The proportion of patients in this subset who showed testosterone levels >1.735nmol/L 48 hours after the second injection (on Day 171 and beyond if testosterone levels >1.735nmol/l on Day 171) is summarized below.

<table>
<thead>
<tr>
<th>Day</th>
<th>171 N (%)</th>
<th>173 N (%)</th>
<th>176 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Castrated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% exact binomial CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (3.33)%</td>
<td>2 (3.33)%</td>
<td>1 (1.67)%</td>
<td></td>
</tr>
<tr>
<td>(0.4% : 11.5%)</td>
<td>(0.4% : 11.5%)</td>
<td>(0.0% : 8.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Two patients in total showed testosterone levels >1.735nmol/l on Day 171 or beyond. Out of these, only one patient experienced an “acute-on-chronic” phenomenon, with a first testosterone level above the limit of castration (1.97nmol/l) on Day 171, 48 hours after the second triptorelin injection. The second patient showing a testosterone level >1.735nmol/l (12.24nmol/l) on Day 171, had not been castrated after the first injection.

On Day 173, none of the two patients mentioned above was castrated.

On Day 176, one patient was castrated, but the other patient still had a testosterone level >1.735 nmol/l. This latter patient achieved and maintained castration level from Day 197 until the end of the study.

Efficacy conclusions for study
Primary efficacy objectives
The study concluded that triptorelin 6-month formulation was effective in inducing and maintaining chemical castration in patients suffering from prostate cancer, as evidenced by 117 of the 120 study subjects (97.5%) in the ITT population being castrated by Day 29, and 107 out of 115 (excluding the five major protocol violations) maintained castration from Day 57 to 337.
There is further discussion on the eight patients who did not maintain castration from 2 to 12 months. Five of these patients had only isolated escapes, three of which were minimal (1.94, 1.97 and 2.33), and none were associated with a rise in prostate specific antigen.

Three patients had clear clinical failures, two patients having escaped castration, and one failing to achieve castration at any point. Comment is made on the fact that this patient was severely obese with a body mass index of 40.2 kg/m² and regarding the possibility that triptorelin release may have been sub-optimal.

**Secondary Efficacy Objectives**
- All patients had an increase in lutinising hormone ≥1.0IU/l from 0 to 2 hours after the first Triptorelin injection. After the 2nd injection, 117 of the 119 (excluding one patient from initial ITT who died before receiving the 2nd injection) patients had a rise in lutinising hormone of ≤1.0IU/l. Two patients had a rise above 1.0 IU/l - one patient with a rise of 1.1IU/L and another with arise of 15.2IU/L, having never achieved a castration level with the first injection. It was concluded that desensitisation of the pituitary gonadotrophin releasing hormone receptors was achieved following the first injection and was maintained when the second injection was given on Day 169.
- The mean percentage change in prostate specific antigen for the baseline to the end of treatment was 82.3% in the ITT population. 93 patients in the ITT population (80.9%) had normal prostate specific antigen values (<4µg/L) at the end of the study.
- In the subset of 60 patients, two (3.3%) patients were not castrated on Day 171, 48 hours after the second triptorelin injection and Day 173 and only one (1.7%) of these patients was not castrated on Day 176. Among these two patients, only one patient presented a minimal “acute-on-chronic” phenomenon (maximum testosterone level 1.97 nmol/L on Day 171), the second patient having never been castrated after the first injection.

Comparison of the primary efficacy results with the results of the studies E28 52014 701, AND DEB-96-TRI-01 is presented in section 2.6 and 2.8.

**2.4 SUPPORTIVE STUDIES**
The pharmacokinetic/pharmacodynamic data and efficacy results of the pilot and pivotal studies (DEB-TRI6M-201 and DEB-TRI6M-301) are compared with the data from the clinical study of the 1-month and 3-month Ipsen formulations (E28 52014 701).

The clinical overview discusses the results of the DEB-TRI6M-301 study in comparison with the data from the DEB-96-TRI-01 study (first phase study for the 3-month formulation).

**2.5 CLINICAL STUDIES IN SPECIAL POPULATIONS**
None submitted.

**2.6 COMBINED DATA AND META-ANALYSES**
Key Efficacy Results from Studies of Triptorelin (ITT) - Table taken from Clinical Overview
## Efficacy Endpoint | DEB-TRI6M-301 6-month | DEB-96-TRI-01 1st phase 3-month | DEB-96-TRI-01 1st phase 1-month
--- | --- | --- | ---
Patients castrated 28 days after injection, % (n/N) (95% confidence interval) | 97.5% (117/120) (92.9%-99.5%) | 97.7% (167/171) (94.1%-99.4%) | 92.7% (152/164) (87.6%-96.2%)
Patients maintaining castration from Days 57-337, % (n/N) (95% confidence interval) | 93.0% (107/115) (86.8%-97.0%) | not available | not available
Patients maintaining castration from Days 57-253, % (95% confidence interval) | 94.1% (89.9%-98.4%) Months 2-9 | 94.4% (90.9%-98.0%) Months 2-9 | 94.2% (90.6%-97.9%) Months 2-9
Patients with ≤1.0 IU/l increase in LH from 0-2h after the 2nd injection, % (n/N) | Day 169: 98.3% (117/119) | Day 85: 92.7% (153/165) Day 169: 91.7% (143/156) | Day 85: 97.4% (152/156) Day 169: 98.0% (146/149)
Patients showing “acute-on-chronic” phenomenon, i.e., escape from castration 48h after the second injection, % (n/N) | 1.7% (1/59) | 0% (0/20) | 0% (0/14)
Group median change in PSA from baseline to Week 24 | 96.9% | 95.8% | 97.0%
Group median change in PSA from baseline to end of study | 96.4% (Week 48) | 96.8% (Week 36) | 97.6% (Week 36)

a. Calculation excludes 5 patients who discontinued study due to no-drug related causes
b. Cumulative maintenance of castration was calculated using Kaplan-Meier survival analysis
c. Assessed in 60 patients, calculation excludes 1 patient who never achieved castration
d. Cumulative maintenance of castration calculated using Kaplan-Meier survival analysis.

### 2.7 STATISTICAL ASSESSMENT OF EFFICACY

**Statistical Assessor’s Comment:**

The overall design of the trial could be acceptable for this indication, although this is a matter of clinical judgement. Although the study is uncontrolled and not blinded, the pharmacological endpoint used is robust to potential biases that could be introduced by this trial design.

The patient disposition has been sufficiently well-described. The statistical methods used to analyse this trial are acceptable. There is very little missing data and the sensitivity analyses do not suggest that there are any concerns regarding this.

It is a matter of clinical judgement as to whether the confidence limit of 92.9-99.5% rules out all clinically relevant values for the castration rate.

### 2.8 ASSESSORS’ OVERALL CONCLUSIONS ON CLINICAL EFFICACY

Clinical efficacy - as determined by the castration rates at 28 days; percentage of patients maintaining castration (Day 57-337), achieved by the 6-month formulation in the pivotal study - is comparable to the results achieved in the studies with the 1-month and 3-month Debiopharm formulations. This is presented in Section 2.6. The study conducted was not a comparative study, and the comparison is with data...
obtained from different studies. The applicant has provided a rationale for conducting a non-comparative pivotal study, which has been accepted. Such studies have been used in the United States and eleven EU countries to obtain approval for triptorelin products. With regards to safety, the vast majority of the adverse effects caused by triptorelin are linked to its pharmacological effect, i.e. testosterone suppression. The active ingredient (triptorelin) and the pharmaceutical form of the new 6-month formulation are the same as the triptorelin 1- and 3-month formulations. Despite the difference in duration of assessment periods, the 6-month formulation has a comparable safety profile to that of the 1-month and 3-month formulations. Therefore, it is deemed sufficient to assess the safety profile of the new formulation by comparing it to those observed in the previous pivotal study with the triptorelin 1- and 3-month formulations, as well as with the post-marketing experience with these formulations.

From the Study E28 52014 701, with the 1-month and 3-month Ipsen formulations, the percentage of patients achieving castration at 28 days and 84 days; and the percentage of patients maintaining castration at Day 91 is presented below. The castration rate of 100% with the 3-month formulation and 91% with the 1-month formulation is compared to the castration rate of 97.5% with the 6-month formulation. Direct comparison with the 6-month formulation is not available in terms of patients maintaining castration for longer periods. The applicant has provided a suitable discussion and has justified that the results with 6 months of treatment with Decapeptyl SR 11.25mg are comparable to 6 months treatment with Decapeptyl SR 22.5mg, in terms of maintenance of castration.

There were no differences found with regards to the action of triptorelin related to ethnic origin and age. The intended target population is the one studied in the submitted pivotal clinical study. There was higher percentage of failure rates in both the ITT and PP population, with body mass index >25 kg/m². However, an exploratory subgroup analysis of data from the 6-month study to assess the potential impact of BMI on the achievement and maintenance of castration did not reveal any clinically significant differences between the groups (BMI ≥25 kg/m² and BMI <25 kg/m²).

### 3 CLINICAL SAFETY

#### 3.1 INTRODUCTION

The safety profile of triptorelin 6-month formulation is based on the non-comparative pivotal study DEB-TRI6M-301, involving 120 patients exposed to the study drug for 48 weeks. The baseline characteristics of the patients relevant to the safety, highlighted in the clinical overview were as follows:

- 28% of patients had rising prostate specific antigen as the only evidence of disease progression
- Prevalence of hypertension in the study population was 62%
- Incidence of diabetes was 10%
- Incidence of hypercholesterolemia was 14%
- Impaired renal function (creatinine clearance <60ml/min) was present in 24% of patients
- Abnormal hepatic test evidenced by alanine aminotransferase (ALT) > upper limit of normal (ULN) was present in 14% of patients.
The clinical overview briefly reviewed the safety profile of triptorelin, determined from the clinical study with the 1-month and 3-month Ipsen formulations, for descriptive comparison. The mean time since diagnosis in these studies was shorter compared to the pivotal study for the 6-month formulation.

3.2 PATIENT EXPOSURE
In the pivotal study, with the 6-month formulation, 117 of the 120 patients (97.5%) were exposed to 48 weeks of treatment with a cumulative dose of 45 mg of Triptorelin.

The mean extent of exposure in the Safety Population was 44.8mg and the mean treatment duration was 47.8 weeks.

<table>
<thead>
<tr>
<th>Extent of Exposure [mg]</th>
<th>Safety N=120</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>120</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>44.81 (2.05)</td>
</tr>
<tr>
<td>SEM</td>
<td>0.19</td>
</tr>
<tr>
<td>CV</td>
<td>4.58</td>
</tr>
<tr>
<td>Median</td>
<td>45.00</td>
</tr>
<tr>
<td>Min - Max</td>
<td>22.50 - 45.00</td>
</tr>
<tr>
<td>95%[LowerCI; UpperCI]</td>
<td>(44.44 ; 45.18)</td>
</tr>
</tbody>
</table>

The E28 52014 701 study, in comparison had 36 patients of the 3-month formulation group who received a minimum dose of 11.25 mg of Triptorelin in one IM injection; and 35 patients in the 1-month formulation group who received a dose of 3 mg of Triptorelin in one IM injection every 28 days during 3 months.

3.3 DEATHS
There were three deaths that occurred during the course of the study. Two of the deaths were due to progression of the prostate cancer, both of which were detected around Day 168, at the time of the second injection of triptorelin. Both patients had progression of prostate cancer despite castration levels of testosterone.

The third fatal outcome occurred in a 65-year-old subject with a history of cerebrovascular accident, coronary bypass and coronary stent, as well as hypertension, hypercholesterolemia and insomnia. The death occurred at home and, in view of the history and high risk of coronary artery occlusion, the probable cause of death was considered to be a myocardial infarction.

All three deaths were assessed by the investigator and the company to have no reasonable causal relationship to the study drug.

3.4 SERIOUS ADVERSE EVENTS
There were 17 serious adverse events noted in 17 patients (14.2%). All these adverse events were assessed by the investigator and the company to have no reasonable causal relationship to the study drug.
A listing of the deaths and serious adverse events is given in the table below:

<table>
<thead>
<tr>
<th>PT</th>
<th>Patient</th>
<th>Severity</th>
<th>Outcome of event</th>
<th>Seriousness</th>
<th>Relationship to treatment</th>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE</td>
<td>05610</td>
<td>SEVERE</td>
<td>Recovered</td>
<td>YES</td>
<td>NRCR</td>
<td>NA</td>
</tr>
<tr>
<td>MYOCARDIAL INFARCTION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANGINA PECTORIS</td>
<td>08608</td>
<td>MODERATE</td>
<td>Recovered</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
<tr>
<td>ATRIAL FLUTTER</td>
<td>11623</td>
<td>SEVERE</td>
<td>Recovered</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
<tr>
<td>DEPRESSION</td>
<td>11614</td>
<td>MODERATE</td>
<td>Sequelae</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
<tr>
<td>DIABETES MELLITUS</td>
<td>11617</td>
<td>MILD</td>
<td>Sequelae</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
<tr>
<td>DIABETIC NEUROPATHY</td>
<td>05611</td>
<td>SEVERE</td>
<td>Not yet recovered</td>
<td>YES</td>
<td>NRCR</td>
<td>NA</td>
</tr>
<tr>
<td>HAEMATURIA</td>
<td>11605</td>
<td>MILD</td>
<td>Recovered</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
<tr>
<td>METASTASES TO BONE</td>
<td>08609</td>
<td>SEVERE</td>
<td>Sequelae</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
<tr>
<td>MYOCARDIAL INFARCTION</td>
<td>11615</td>
<td>SEVERE</td>
<td>Fatal</td>
<td>YES</td>
<td>NRCR</td>
<td>NA</td>
</tr>
<tr>
<td>OBSTRUCTIVE UROPATHY</td>
<td>03606</td>
<td>SEVERE</td>
<td>Sequelae</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
<tr>
<td>PENIS CARCINOMA</td>
<td>02601</td>
<td>MODERATE</td>
<td>Recovered</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
<tr>
<td>NEPHRONIA</td>
<td>11606</td>
<td>SEVERE</td>
<td>Recovered</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
<tr>
<td>PROSTATE CANCER</td>
<td>05612</td>
<td>SEVERE</td>
<td>Fatal</td>
<td>YES</td>
<td>NRCR</td>
<td>NA</td>
</tr>
<tr>
<td>PROSTATE CANCER METASTATIC</td>
<td>05614</td>
<td>SEVERE</td>
<td>Fatal</td>
<td>YES</td>
<td>NRCR</td>
<td>NA</td>
</tr>
<tr>
<td>SKIN LACERATION</td>
<td>11621</td>
<td>SEVERE</td>
<td>Not yet recovered</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
<tr>
<td>SOFT TISSUE INJURY</td>
<td>03601</td>
<td>SEVERE</td>
<td>Sequelae</td>
<td>YES</td>
<td>NRCR</td>
<td>None</td>
</tr>
</tbody>
</table>

Note: NRCR = No reasonable causal relationship (Investigator’s assessment)

**Clinical Assessor’s Comment:**

The serious adverse events reported, such as acute myocardial infarction, angina pectoris, atrial flutter, diabetes mellitus, and diabetic neuropathy have been classed as “no reasonable causal relationship (NRCR)”. There are concerns regarding the metabolic effects of long-term gonadotrophin releasing hormone use, leading to cardiovascular disease and diabetes mellitus.

In the triptorelin 6-month formulation pivotal study (DEB-TRI6M-301) the cardiovascular serious adverse events comprised 24% (4/17) of the total serious adverse events, which is not higher than the incidence expected in a population of elderly men not treated with gonadotrophin releasing hormone analogues.

Data from literature remains inconclusive, as these cardiovascular adverse effects could be explained by metabolic changes that were observed during androgen deprivation therapy, but seem to have different features when compared to the classically defined metabolic syndrome. However, this observed increase in cardiovascular morbidity is apparently not reflected by a clear increase in cardiovascular mortality.

The applicant has provided a case-by-case description of the serious adverse events reported. All the patients involved have a previous history of cardiovascular disease and/or diabetes.
3.5 COMMON ADVERSE EVENTS

115 patients (95.8%) out of the 120 patients reported a total of 512 adverse events during the study. An overview is presented in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Number of patients with AEs</th>
<th>% of patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with adverse events</td>
<td>115</td>
<td>95.83</td>
<td>512</td>
</tr>
</tbody>
</table>

**Intensity**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients with AEs</th>
<th>% of patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>104</td>
<td>86.67</td>
<td>378</td>
</tr>
<tr>
<td>Moderate</td>
<td>57</td>
<td>47.50</td>
<td>110</td>
</tr>
<tr>
<td>Severe</td>
<td>17</td>
<td>14.17</td>
<td>24</td>
</tr>
</tbody>
</table>

**Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients with AEs</th>
<th>% of patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td>90</td>
<td>75.00</td>
<td>241</td>
</tr>
<tr>
<td>Not yet recovered</td>
<td>103</td>
<td>85.83</td>
<td>260</td>
</tr>
<tr>
<td>Sequelae</td>
<td>5</td>
<td>4.17</td>
<td>5</td>
</tr>
<tr>
<td>Fatal</td>
<td>3</td>
<td>2.50</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>1.67</td>
<td>3</td>
</tr>
</tbody>
</table>

**Relationship**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients with AEs</th>
<th>% of patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reasonable causal relationship</td>
<td>100</td>
<td>83.33</td>
<td>338</td>
</tr>
<tr>
<td>Reasonable causal relationship</td>
<td>97</td>
<td>80.83</td>
<td>165</td>
</tr>
<tr>
<td>Unassessable</td>
<td>4</td>
<td>3.33</td>
<td>9</td>
</tr>
</tbody>
</table>

**Serious adverse events**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients with AEs</th>
<th>% of patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>3</td>
<td>2.50</td>
<td>3</td>
</tr>
</tbody>
</table>

As summarised in the table above, 115 out of the 120 patients (95.8%) reported at least one treatment-emergent adverse event (TEAE; any new, undesirable medical occurrence or change in an existing condition in a patient that occurred during or after the study drug administration, whether or not considered to be drug-related). Out of the adverse events, 378 mild adverse events were reported by 104 patients (86.7%), 110 moderate adverse events were reported by 57 patients (47.5%) and 24 severe adverse events were mentioned by 17 patients (14.2%).

165 of the adverse events reported in 97 patients (80.8%) were considered related to the study medication.

**Table 23. AEs with more than 10% incidence**

<table>
<thead>
<tr>
<th>PT Name</th>
<th>SOC Name</th>
<th>Number of patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>13 (10.83)%</td>
<td>17</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Reproductive system and breast disorders</td>
<td>12 (10.00)%</td>
<td>12</td>
</tr>
<tr>
<td>Hot flush</td>
<td>Vascular disorders</td>
<td>87 (72.50)%</td>
<td>98</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Vascular disorders</td>
<td>17 (14.17)%</td>
<td>18</td>
</tr>
<tr>
<td>Influenza</td>
<td>Infectious and infestations</td>
<td>19 (15.83)%</td>
<td>24</td>
</tr>
</tbody>
</table>

The most frequently reported TEAEs, occurring in ≥10% of patients, were hot flushes (72.5%), influenza (15.8%), hypertension (14.2%), back pain (10.8%), and erectile dysfunction (10.0%). Approximately 30% of TEAEs reported by 97 (80.0%) patients were considered to have a reasonable relationship to study treatment. The most common drug-related TEAEs, occurring in ≥2% of patients, were hot flushes (71.7% of the patients), erectile dysfunction (10.0%), testicular atrophy (7.5%), and fatigue (4.2%).

Commonly reported TEAEs that are likely related to the underlying prostate cancer include prostate cancer worsening (3.3% of the patients receiving the 6-month
formulation), back pain (10.8%), bone pain (3.3%), pain in extremity (7.5%), dysuria (1.7%), haematuria (2.5%), urinary incontinence (3.3%), urinary retention (5.0%), and urinary tract infection (9.2%).

In comparison, the clinical overview details the trial with the 1-month and 3-month Ipsen formulations. The most common side-effect was hot flushes (51 patients, 72% of trial population). Impotence and loss of libido were reported in 12 (67%) and 14 (70%) patients among those not reporting this at presentation. 42% of patients reported other adverse events (15 patients in each group); four of which were serious with one death in the 1-month formulation due to acute prostatitis.

3.6 DISCONTINUATION DUE TO ADVERSE EVENTS
The patient that died during the course of the study, due to a probable myocardial infarction, did not receive the 2nd dose of Triptorelin, as the event occurred before Day 169.

3.7 LABORATORY FINDINGS
Laboratory parameters at pre-treatment, baseline (Day 1), Day 169, Day 337 and the changes from baseline to Day 169 and Day 337 are presented as descriptive statistics.

Shift tables based on laboratory normal ranges were presented for each laboratory parameter between pre-treatment and worst case on-treatment. Shift was defined as a direction of change between pre- and on-treatment, among the three categories: "Low" (below normal laboratory range), "Normal" (within normal laboratory range), and "High" (above normal laboratory range). The table below presents shift tables for all laboratory parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Worst Case</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (%)</td>
<td>Normal (%)</td>
</tr>
<tr>
<td>ALAT (GPT)</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>ASAT (GOT)</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine (Plasma)</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0</td>
</tr>
<tr>
<td>Glucose</td>
<td>Low</td>
<td>7 (26.9%)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>11 (41.1%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>15 (55.2%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Low</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Platelets Count</td>
<td>Low</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Prothrombin Time</td>
<td>Low</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>6 (21.3%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Red Blood Count</td>
<td>Low</td>
<td>6 (21.3%)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>White Blood Count</td>
<td>Low</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

The parameters that exhibited changes from normal to low or high in more than 10% of patients were glucose (18.3% change from normal to high), prothrombin time (14.0% change from normal to high), haemoglobin (12.9% change from normal to low) and red blood count (12.3% change from normal to low).
3.7.1 ECG and QTc
There is no analysis of ECG for patients on the study. However, there is data in literature to suggest that treatment with gonadotrophin releasing hormone agonists may prolong the QT interval.

3.7.2 Other
Blood Pressure:
Descriptive statistics for vital signs at each timepoint, for the worst case on treatment and change from baseline to worst case on-treatment were presented.

Shift tables are presented for each vital sign between baseline and worst case on treatment (refer to the study report for further details). The limits for defining the three shift categories refer to the magnitude of the change from baseline to worst-case on-treatment. For blood pressure, the three categories are defined as: “Low” (decrease from pre-treatment >20mmHg), “Normal” (change from pre-treatment within ± 20mmHg) and “High” (increase from pre-treatment >20mmHg). The limit is set for heart rate to 20 beats per minute. The following section summarizes these changes:

• Diastolic blood pressure: 28 patients had a change defined as "low", 71 patients remained within normal range, and 21 patients had a change to “high”.
• Systolic blood pressure: 57 patients had a change defined as "low", 19 patients remained within normal range, and 44 patients had a change to “high”.
• Heart rate: 17 patients had a change defined as "low", 81 patients remained within normal range, and 22 patients had a change to “high”.

The systolic blood pressure was the only vital signs that presented abnormal changes (to “low” or “high”) in more than 50% of patients. There was no systematic tendency in the systolic blood pressure change.

Body Weight:
By Day 169, 23.1% of patients showed with an abnormal increase, 8.6% an abnormal decrease and 68.4% showed no change in body weight.

By Day 337, 36.3% of patients showed with an abnormal increase, 10.6% an abnormal decrease and 53.1% showed no change in body weight.

3.8 SAFETY IN SPECIAL POPULATIONS
No data submitted, and none are required.

3.9 DRUG-SPECIFIC SAFETY CONSIDERATIONS
No data submitted

3.10 SAFETY RELATED TO INTERACTIONS
The clinical study report lists previous prostate cancer medications and concomitant medications used by the patients. However, no safety issues related to interaction have been highlighted.

3.11 PHARMACOVIGILANCE
The MHRA considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant
has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable risk management plan has been submitted for these products.

3.12 RISK MANAGEMENT PLAN
A list of safety concerns regarding this product and the activities taken is presented below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed Pharmacovigilance Activity (routine and additional)</th>
<th>Risk Minimisation Activity (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone loss</td>
<td>Routine pharmacovigilance</td>
<td>Mention in the SPC Section 4.4 (Warning and precautions): “In adults, the prolonged use of GnRH analogues may lead to bone loss which enhances the risk of osteoporosis” Mentions in the SPC Section 4.8: “The use of synthetic GnRH agonists to treat prostate cancer may be associated with increased bone loss and may lead to osteoporosis and increases the risk of bone fracture”</td>
</tr>
<tr>
<td>Metabolic changes</td>
<td>Routine pharmacovigilance</td>
<td>Mention in the SPC Section 4.4 (Warning and precautions): “In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance), or an increased risk of cardiovascular disease during androgen deprivation therapy. Patients at high risk for metabolic or cardiovascular diseases and receiving androgen deprivation therapy for more than 6 months should be monitored at appropriate intervals not exceeding 3 months.”</td>
</tr>
<tr>
<td>Patients at high risk for metabolic or cardiovascular disease and receiving androgen deprivation therapy for more than 6 months should be monitored at appropriate intervals not exceeding 3 months.</td>
<td>Routine pharmacovigilance</td>
<td>Mention in the SPC Section 4.4 (Warning and precautions): “In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance), or an increased risk of cardiovascular disease during androgen deprivation therapy. Patients at high risk for metabolic or cardiovascular diseases and receiving androgen deprivation therapy for more than 6 months should be monitored at appropriate intervals not exceeding 3 months.”</td>
</tr>
</tbody>
</table>

3.13 ASSESSOR’S OVERALL CONCLUSIONS ON CLINICAL SAFETY
Triptorelin has been marketed for 22 years. The safety profile of triptorelin is well-known. The incidence of serious adverse events in the pivotal study was 14.2%. The serious adverse events reported include acute myocardial infarction, angina pectoris, atrial fibrillation, diabetes mellitus and diabetic neuropathy. The applicant has provided a case-by-case description of the serious adverse events reported. All the patients involved have a previous history of cardiovascular disease and/or diabetes.

The three deaths that occurred were reported as unrelated to the study medication. The one death presumed to be due to myocardial infarction, in a patient with a history of ischaemic heart disease.
The majority of the non-serious adverse events were related to androgen deprivation. Some of the common adverse events reported were related to the underlying prostate cancer. The incidence of adverse events was comparable to the incidence of adverse events seen with the trial for the 1-month and 3-month formulations.

Local tolerance of the 6-month depot formulation was good and no drug hypersensitivity reaction has been observed.

The pivotal study for the 6-month formulation, has noted a variation in the systolic blood pressure, though there was no systematic tendency to the systolic blood pressure change. Furthermore, the study also identified an increase in the blood sugar levels from normal to high in 10% of patients. The incidence of cardiac events in the trial was low and not considered related to the study medication.

In consideration of the prolonged treatment duration for which this drug is intended, the SmPC carries a warning highlighting the increased risks of prolonged androgen deprivation, and the necessity to monitor patients regarding diabetes, cardiac disease, and effect on bone density. There is also a statement on the possibility of QT-interval prolongation.

A suitable Pharmacovigilance System and Risk Management Plan have been submitted for this application.

4 EXPERT REPORT
The clinical expert report was written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

5 PRODUCT LITERATURE
5.1 SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The summary of product characteristics is satisfactory and consistent with that for a product of this type.

5.2 PATIENT INFORMATION LEAFLET (PIL)
The patient information leaflet is satisfactory and consistent with the SmPC.

5.3 LABEL
The labelling is satisfactory and is in-line with current regulations.

5.4 APPLICATION FORM
The MAA form is satisfactory.

6 OVERALL CONCLUSION
The grant of a licence is recommended for this product.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
With the exception of one non-clinical study, which investigated the pharmacokinetics of three different formulations of slow-release triptorelin, no new data were submitted and none are required for an application of this type.

EFFICACY
Suitable pharmacokinetic data have been submitted to show that Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection can be considered to be comparable to other currently marketed formulations of triptorelin treatment. Any differences in pharmacokinetics have been discussed and explained, and these have not been observed in the pharmacodynamic data collected.

The pharmacodynamic data shows that, although there is a rise in lutinising hormone and testosterone from the first injection of study product, testosterone levels are greatly reduced after 6 months. Furthermore, the spike in testosterone is not seen with subsequent injections.

Efficacy data show that this product is comparable with other marketed formulations. No differences in efficacy were observed with different ethnic origin, age or body mass index.

SAFETY
No new or unexpected safety concerns arose from this application. The adverse events recorded with the use of Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection are consistent with those seen in other triptorelin-containing products.

The SmPC, PIL and labelling are satisfactory. As this is a 6-month slow-release formulation, suitable statements have been added to the SmPC concerning the effects of long-term androgen depletion.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with triptorelin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
**DECAPEPTYL SR 22.5MG POWDER AND SOLVENT FOR SUSPENSION FOR INJECTION**  
**PL 34926/0013**

**STEPS TAKEN FOR ASSESSMENT**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 27th May 2009.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 25th June 2009.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the quality dossiers on 16th July 2009, and relating to the clinical dossier on 21st December 2009 and 23rd July 2010.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information for the quality dossier on 3rd September 2009 and for the clinical dossier on 26th March 2010 and 23rd August 2010.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 14th September 2010.</td>
</tr>
</tbody>
</table>
A list of non-safety variations of clinical significance are presented below.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/10/2011</td>
<td>II</td>
<td>To update SmPC and PIL by including information related to concomitant and adjuvant treatment to radiotherapy for prostate cancer (see Annex 1).</td>
<td>Granted 24/11/2011</td>
</tr>
<tr>
<td>03/10/2012</td>
<td>II</td>
<td>To update SmPC in order to further define the target patient population and align with current clinical practice and uro-oncology clinical guidelines (see Annex 2).</td>
<td>Granted 02/05/2013</td>
</tr>
<tr>
<td>30/08/2013</td>
<td>II</td>
<td>To update section 4.2 (posology and administration) of the SmPC in order to reflect recent evolutions in the prostate cancer therapeutic armamentarium and current medical practice, in accordance with official international and European treatment guidelines. To also update section 4.8 (undesirable effects) of the SmPC to include the Yellow Card adverse reactions reporting scheme text (see Annex 3).</td>
<td>Granted 01/05/2014</td>
</tr>
</tbody>
</table>
Annex 1

Reference(s): PL 34926/00013 - 0007
Product(s): Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection
Marketing Authorisation Holder: Ipsen Limited
Active Ingredient(s): Triptorelin Pamoate

Reason
To update SmPC and PIL by including information related to concomitant and adjuvant treatment to radiotherapy for prostate cancer.

Supporting Evidence
Updated sections 4.1 (Therapeutic Indications) and 5.1 (Pharmacodynamic Properties) of the SmPC have been provided. Updated PIL provided to include details of concomitant and adjuvant treatment to radiotherapy for prostate cancer treatment.

The following four studies have been listed by the applicant and the publications provided as references. All these studies were conducted using Goserelin 3.6 mg. These studies are discussed before the pivotal study in this assessment report, to set a background and to discuss the use of lutinising hormone releasing hormone (LHRH) agonists as adjuvant to definitive radiotherapy in the treatment of prostate cancer.

Radiation Therapy Oncology Group (RTOG) 85-31 Study:

Design:
This Phase III, prospective trial was designed to evaluate the potential benefit of androgen suppression with Zoladex (goserelin) as adjuvant to standard external beam irradiation, in comparison to the use of androgen suppression therapeutically at the time of relapse following standard external beam radiotherapy, in patients with locally advanced prostate cancer.

Patient Population:
Between 1987 and 1992, 977 patients were enrolled into the trial. 488 patients were randomised to treatment Arm I (radiotherapy and adjuvant goserelin); and 489 were randomised to treatment Arm II (radiotherapy alone with goserelin at relapse).

Patients eligible for this trial were those with histologically confirmed adenocarcinoma of the prostate, with regional lymphatic involvement (pN+) or gross extension of the palpable primary tumour beyond the prostate (T3). Patients with clinical T1 and T2 tumours were eligible if there was radiological or histological evidence of regional lymph nodal involvement, including external iliac, internal iliac, common iliac, and periaortic lymph nodes. Patients who had had previous prostatectomy were also eligible, if there was documented penetration through the prostate capsule to the margin of resection and/or the seminal vesicle. These patients were required to have a Karnofsky performance status greater than 60%.

Treatments:
Goserelin was the LHRH agonist used in this trial, and was administered a dose of 3.6 mg starting during the last week of radiotherapy, in Arm I; and at the time of relapse in Arm II. Treatment was continued indefinitely or until signs of progression.
Radiotherapy was administered with a dose of 44-46 Gy to the initial target, which varied depending on the extent of disease/lymph nodal regions involvement. The prostatic target volume received a further boost of 20-25 Gy, bringing the total dose to 65-70 Gy.

**Endpoints:**
The endpoints studied were overall survival, disease free survival, and time to treatment failure.

**Results:**

With a median follow-up of 5.6 years:

- The 8 year local failure rate was 23% for Arm I compared to 37% for Arm II (p<0.0001).
- The distant metastases rate was 27% for treatment Arm I and 37% for treatment Arm II (p<0.0001).
- Disease free survival (no clinical evidence of disease, NED), and disease free survival including biological DFS (PSA≤1.5, bNED) were both statistically significant in favour of treatment in Arm I (p<0.0001).
- Cause specific mortality and overall survival were not statistically different between the two treatment arms.
- Subset analysis of Gleason 8-10 patients who did not undergo prostatectomy showed that there was a statistically significant improvement in the in both absolute survival (p=0.036) and cause-specific mortality (p=0.019) favouring the treatment with radiotherapy and adjuvant goserelin.

With a median follow-up of 7.6 years for all patients and 11 years for living patients:

- The 10-year absolute survival rate was significantly greater in Arm I than for the Arm II: 49% vs. 39% (p=0.002).
- The 10-year local failure rate was 23% for treatment Arm I and 38% for treatment Arm II (p<0.0001).
- The 10-year incidence rate of distant metastases was 24% for treatment Arm I and 39% for treatment Arm II (p<0.001).
- The 10-year incidence rate of cause specific mortality was 16% for treatment Arm I and 22% for treatment Arm II (p=0.0052). On subgroup analysis, the results appeared to be significant only in the patients with Gleason scores 8-10.

**Patients with lymph nodal metastases:**
The best form of treatment and the role of local therapy for pN+ patients were controversial. In trying to address this question, with radiation therapy as the local-regional treating modality, the Radiation Therapy Oncology Group (RTOG) published a subset analysis of the trial 85-31. This subset analysis included 173 patients with biopsy-proven pathologically involved lymph nodes (pN+) who were randomly assigned to receive either radiation alone (n=75) or radiation plus immediate androgen suppression (LHRH agonist; n = 98).

In the above subset analysis, with a median follow-up of 6.5 years for all patients and 9.5 years for living patients, estimated progression-free survival with prostate-specific antigen (PSA) level less than 1.5 ng/mL at 5 and 9 years was 54% and 10%, respectively, for patients who received immediate LHRH agonist; compared to 33% and 4% for patients who received radiation alone with hormonal manipulation instituted at time of relapse (p<0.0001).
Multivariate analysis revealed radiation therapy and immediate hormonal manipulation as having a statistically significant impact on all end points analyzed: absolute survival, disease-specific failure, metastatic failure, biochemical control with PSA less than 4 ng/mL, as well as biochemical control with PSA less than 1.5 ng/mL.

Assessor’s Comments:

- This study showed a beneficial effect on survival, with addition of Goserelin as an adjuvant to definitive radiotherapy, in the treatment of locally advanced prostate cancer. Subset analyses show that the effect is statistically significant in patients with high Gleason scores (≥7).
- This study did include patients with more extensive lymph nodal involvement than the other studies discussed below, and subset analyses of patients with lymph nodal metastases showed benefits with improvements in progression free survival, disease control and absolute survival favouring the adjuvant use of Zoladex.

2.1.1 EORTC 22863 Study:

**Design:**
This was a prospective randomised phase III trial which *compared external irradiation alone, with external irradiation combined with long term LHRH agonist therapy, in the treatment of locally advanced prostate cancer.*

**Patient Population:**
Between 1987 and 1995, *415 patients* were randomly assigned radiotherapy alone or radiotherapy plus immediate androgen suppression. Eligible patients had T1–2 tumours of WHO grade 3 or T3–4 N0–1 M0 tumours; the median age of participants was 71 years (range 51–80).

**Treatments:**
In both treatment groups, 50 Gy radiation was delivered to the pelvis over 5 weeks and 20 Gy over 2 weeks as a prostatic boost.

In the combined treatment arm, goserelin (3·6 mg subcutaneously every 4 weeks) was started on the first day of irradiation and continued for 3 years; cyproterone acetate (150 mg orally) was given for 1 month starting 1 week before the first goserelin injection.

**Endpoints:**
The primary endpoint was clinical disease-free survival. Analyses were by intention to treat.

**Results:**
The results of this trial were published at several time points.

At a median follow-up of 45 months (*ref: Bolla M et al, 1997; NEJM*),

- Kaplan–Meier estimates of overall survival at five years were 79 percent (95% CI: 72- 86%) in the combined-treatment group and 62% (95%CI: 52- 72%) in the radiotherapy group (P<0.001).
- The proportion of surviving patients who were free of disease at five years was 85% (95%CI: 78 to 92%) in the combined treatment group and 48% (95%CI: 38 to 58%) in the radiotherapy group (p<0.001).
At a median follow-up of 66 months (range 1–126) (ref: Bolla M et al, 2002; The Lancet),
- 5-year clinical disease-free survival was 40% (95% CI 32–48) in the radiotherapy-alone group and 74% (95% CI: 67–81%) in the combined treatment group (p=0·0001).
- 5-year overall survival was 62% (95% CI: 52–72%) with radiotherapy alone compared to 78% (95% CI: 72–84%) with the combined treatment (p=0·0002). The respective 5-year specific survivals were 79% (95% CI: 72–86%) and 94% (95% CI: 90–98%).

At a median follow-up of 9.1 years (ref: Bolla M et al, 2008; Int J of Radiation Oncology Biol Phys),
- 192 of the 415 patients had died (112 on RT alone and 80 on combined treatment arm).
- The 10-year overall survival with the combined treatment was 39.8% compared to 58.1% with radiotherapy alone (HR=0.60; CI:0.45-0.80; p=0.0004).
- Clinical progression free survival was also greater with the combined treatment-47.7% compared to 22.7% with radiotherapy alone.
- The distant PFS as well as clinical or biochemical PFS was better with the combined treatment as well.
- The 10 year cumulative incidence of prostate cancer mortality was 31% with radiotherapy alone compared to 11.1% with the combined treatment (HR:0.38, CI: 0.24-0.60; P<0.001).
- The 10 year cumulative incidence of cardiovascular mortality amounted to 8.2% in the combined arm, compared to 11.1% in the radiotherapy alone treated population (HR:1.11, CI: 0.59-2.09; p=0.75).

**Assessor’s Comment:**
- This study showed that addition of 3 years of hormonal treatment, which in this case was Zoladex 3.6 mg 4 weekly, following definitive radiotherapy, improved the overall survival and progression free survival in the studied population (locally advanced prostate cancer, and patients with Grade 3 localised prostate cancer).
- Not all patients had a Gleason score assigned. For over 1/3 of patients in both arms the Gleason scores were unknown. About 1/3 of patients in both arms had a Gleason score ≥7. Subgroup analyses were conducted based on the WHO grade which showed that Grade 3 disease compared to grades 1-2 was an adverse prognostic factor for disease free survival.
- No analyses were conducted based on the Gleason scores. Therefore, a selective benefit as seen in the RTOG 85-31 in patients with Gleason ≥7, cannot be commented on in the results of the EORTC 22863 trial.
- There was no statistically significant difference in the incidence of cardiovascular toxicity.

2.1.2 RTOG 86-10 Study:

**Design:**
This was the first phase III randomised trial to evaluate neoadjuvant androgen deprivation therapy (ADT) in combination with external-beam radiotherapy (EBRT) in men with locally advanced prostate cancer.
Patient Population:
Between 1987 and 1991, 456 patients (median age, 70 years) were enrolled. Eligible patients had bulky (5X5 cm) tumours (T2-4) with or without pelvic lymph node involvement, according to the 1988 American Joint Committee on Cancer TNM staging system. Patients received combined ADT that consisted of goserelin 3.6 mg every 4 weeks and flutamide 250 mg tid for 2 months before and concurrent with EBRT, or they received EBRT alone.

Endpoints:
Study end points included overall survival (OS), disease-specific mortality (DSM), distant metastasis (DM), disease free survival (DFS), and biochemical failure (BF).

Results:
At 8 years, the combined treatment was associated with (ref: Pilepich et al, 2001; Int. J. Radiation Oncology Biol. Phys.):
- an improvement in local control (42 vs. 30%, p=0.016);
- reduction in the incidence of distant metastases (34% vs. 45%; p=0.04);
- improvement in disease free survival (33% vs. 21%; p=0.004);
- improvement in the biochemical disease free survival (PSA<1.5) (24% vs.10%, p=0.0001);
- a decrease in the cause specific mortality (mortality due to prostate cancer) (23% vs. 31%, p=0.05)

Ten-year overall survival estimates (43% with combined therapy vs. 34% with radiotherapy alone) and median survival times (8.7 years with combined therapy vs. 7.3 years with radiotherapy alone) favoured the combined therapy. However, these differences did not reach statistical significance (p=0.12). With the addition of ADT, there were statistically significant improvements in:
- 10-year disease-specific mortality (mortality due to prostate cancer) (23% vs. 36%; p=0.01),
- distant metastases (35% vs. 47%; p=0.006),
- disease free survival (11% vs. 3%; p<0.0001),
- biochemical failure (65% vs. 80%; p<0.0001)

Fatal cardiac events were reported to have occurred in 12.5% (95% CI, 8.0 to 17.0) of patients treated with ADT and EBRT, compared with 9.1% (95% CI, 5.3 to 13.0) in patients treated with EBRT alone (P=0.32).

Assessor’s Comment:
- The RTOG 86-10 study showed an improvement in disease control, as well as the duration of disease control, on addition of androgen deprivation therapy prior to and concomitantly with external beam radiotherapy in patients with locally advanced prostate cancer. The only LHRH agonist used in this study was Goserelin 3.6 mg.
- This benefit with disease control was observed to be significant in patients with a Gleason score of 2-6; whereas there was not statistically significant difference in patients with a Gleason score 7-10.
- There was no statistically significant difference seen in the overall survival.
2.1.3 RTOG 92-02 Study:

**Design:**
This prospective, randomized trial was conducted to determine whether adding 2 years of androgen-deprivation therapy (ADT) improved outcome for patients with locally advanced prostate cancer, electively treated with ADT before and during radiation therapy (RT).

**Patient Population:**
Between June 1992 and April 1995, 1554 patients were randomised.

**Treatments:**
All patients received definitive radiotherapy. All patients received 4 months of treatment with flutamide 250 mg tid and monthly injections of goserelin 3.6 mg subcutaneously, before and until completion of radiotherapy. The patients were then randomised to receive no further therapy (short term androgen deprivation- SDAT-RT arm, n=779); or to receive goserelin 3.6 mg monthly for a further 2 years (long term androgen deprivation- LDAT-RT arm, n=775).

**Results:**
At 5 years there was no statistically significant difference between the overall survival in both arms (80.0% with LDAT compared to 78.5% with SDAT, p=0.73). However, in subset analysis, patients with Gleason score 8 to 10 had a significantly better overall survival on treatment with LDAT-RT (81%) compared to SDAT-RT (70.7%) (p=0.44). In patients with Gleason scores 2 to 7, a significant advantage of the LTAD-RT arm was seen for DFS, with a 5-year rate of 49.4% (range, 44% to 54%) as compared with 31.8% (range, 27% to 36%; P <0.0001) for the STAD-RT arm. (ref: Hanks GE et al, 2003; JCO)

At 10 years, the LTAD-RT group showed significant improvement over the STAD-RT group for all end points except overall survival (ref: Horwitz EM et al, 2008; JCO):
- disease-free survival (22.5% v 13.2%; p<0.0001),
- disease-specific survival (88.79% v 83.9%; p <0.0042),
- local progression (12.3% v 22.2%; p<0.0001),
- distant metastasis (14.8% v 22.8%; p<0.0001),
- biochemical failure (51.9% v 68.1%; p<0.0001),
- Overall survival (53.9% v 51.6%, p<0.36).

A 10 year treatment outcome analyses was conducted for the subgroup of patients with Gleason scores of 8 to 10. An overall survival difference was observed (LDAT vs. SDAT: 45.05% v 39.91%; p=0.0061), as well as in all other end points.
- disease-free survival (20.81% v 9.35%; p<0.0001),
- disease-specific survival (79.81% v 66.91%; p=0.0072),
- local progression (17.77% v 27.26%; p=0.0338),
- distant metastasis (25.56% v 39.69%; p=0.0019),
- biochemical failure (55.95% v 73.87%; p<0.0001),

**Assessor’s Comment:**
- The RTOG 92-02 study showed an improvement in endpoints relating to disease control with the use of long term androgen deprivation with radiotherapy over the use of short term androgen deprivation. The results obtained are again with the
2.2 PIVOTAL TRIAL - EORTC 22961 STUDY:
This is the pivotal study submitted in support of the proposed indication, as this trial involved the use of Decapeptyl SR 3 mg or 11.25 mg in 62.2% of the patients. 30% of the patients received goserelin as the LHRH agonist.

This study compared the use of radiotherapy plus short term androgen suppression, with the use of radiotherapy plus long-term androgen suppression in the treatment of locally advanced prostate cancer.

The study was conducted and sponsored by the European Organisation for Research and Treatment of Cancer (EORTC). Ipsen Pharma provided an educational grant and supplied the LHRH agonist Decapeptyl used for the study, but had no role in the design or conduct of the study; nor in the analysis or interpretation of data, nor in the preparation of the manuscript for publication. The design, data collection, and statistical analysis and interpretation were performed independently at the EORTC headquarters in Brussels.


The investigators state that the study was conducted in compliance GCP Guidelines.

2.2.1 Aim:
The study was conducted to determine whether short-term androgen suppression was non-inferior to long-term androgen suppression, both in terms of overall survival and preservation of the quality of life.

2.2.2 Methods:
Patient Population:
The population included were patients with histologically confirmed prostate adenocarcinoma with:

- T1c to T2a–b, pathological nodal stage N1 or N2, and no clinical evidence of metastatic spread (M0), according to UICC TNM staging;
- or with clinical tumour stages T2c to T4, clinical nodal stages N0 to N2, and no clinical evidence of metastatic spread (M0), according to UICC TNM staging;
- a baseline level of prostate specific antigen (PSA) of up to 40 times the upper limit of the normal range (≤150 ng/mL before complete androgen blockade);
- and a World Health Organization (WHO) performance status of 0 to 2.

Additional criteria were a haemoglobin level of 10 g/dL or more; a white-cell count of 2×10⁹ per litre or more; and a platelet count of 100×10⁹ per litre or more, as well as no
prior treatment for prostate cancer (except hormone therapy for ≤3 weeks) and no previous cancer (except treated basal-cell skin cancer).

The pathological specimens were not centrally reviewed.

**Medical Assessor’s Comment:**

The baseline characteristics of the patients were balanced between the two treatment groups. There are a small proportion of patients for whom the Gleason score is not available, and unlike the previous EORTC trial discussed histological grading based on the older WHO criteria is no longer used.

The patient population chosen for the trial includes T2c to T4 stage disease which includes disease classified as locally advanced, according to certain guidelines. In addition there are patients with T1C to T2b tumours with regional lymph nodal metastases.

A high Gleason score (8-10), which is considered a high risk factor, in addition to high PSA, and T3-T4 disease status; is not considered in the inclusion criteria. The population chosen does not appear to include a patient group with “high-risk localised disease”.

**Treatments/ Interventions:**

**Radiotherapy**

All patients received three-dimensional conformal radiotherapy, with a three-field or four-field isocentric beam setup based on a computed tomographic (CT) definition of two planned target volumes. Treatment was provided once a day, 5 days a week, for 7 weeks, at a dose of 50 Gy for the first planned target volume and an additional dose of 20 Gy for the second planned target volume.

**Hormonal Therapy**

The first 6 months of androgen suppression consisted of complete androgen blockade with an LHRH agonist, initiated on the first day of irradiation, and an antiandrogen agent (750 mg of flutamide per day or 50 mg of bicalutamide per day), initiated 1 week before the start of treatment with the LHRH agonist.

The patients assigned to long-term suppression continued to be treated with the same LHRH agonist but without the antiandrogen for another 2.5 years.

From March 1, 1998, through July 15, 1999, the LHRH agonist triptorelin was used exclusively and administered intramuscularly once a month; thereafter, when a new 3-month formulation became available, triptorelin was administered every 3 months.

Patients were stratified according to institution, clinical tumour stage, nodal stage, initial PSA, and Gleason’s score.

**Primary End-Point:**

The primary end-point was to overall survival which was defined as the time from randomisation to death from any cause. A hazard ratio of 1.35 or less was used to establish the non-inferiority of short-term suppression to long-term suppression. The plan was to base this test on a total of 275 deaths for 80% power at the one-sided 5% significance level and to execute the test 5 years after the last patient entered the study.
Secondary End-Points:
The secondary end-points were survival free of clinical progression, survival free of regional and distant metastases, and survival free of biochemical progression.

Clinical progression-free survival was defined as the time from randomization to clinical disease progression or death from any cause. Clinical progression was defined as palpable enlargement of an existing abnormality or regrowth of a previously regressed prostate gland by 25% or more, assessed on the basis of the product of its two largest diameters, or urethral obstruction. Regional and distant metastases were documented by imaging studies. Confirmation of local or regional progression by biopsy was not considered in the analysis of these end points.

Biochemical progression was defined as a PSA level of more than 1.5 ng/mL and an increase in the PSA level on two successive occasions at least 3 months apart.

Statistical Analysis and Considerations:
For the purposes of this trial, external radiotherapy associated with 3 years of adjuvant hormonal therapy was considered as the standard treatment based on the results of EORTC trial 22863, with an estimated 5-year overall survival rate of 80%. The aim of the trial 22961 was to evaluate if a shorter hormonal therapy gave a non inferior survival compared to long term hormonal treatment. The 5-year survival rate in the reference arm was estimated at 80%. Non-inferiority was defined as a relative risk not greater than 1.35. This corresponds to a decrease of the 5-year survival rate by at most 6%, from 80% to 74%. Based on that hypothesis, it was estimated that a total of 275 deaths need to be observed to prove this definition of non-inferiority with a power of 80%, and a one-sided type I error rate of 5% (α=0.05). To observe those events, it was projected to randomize a total of 966 patients over a 5-year time period. It was estimated that a follow-up period of 5 years after the last inclusion was required to observe the required number of events.

Overall survival was assessed with the use of the modified log-rank test for non-inferiority. Hazard ratios and confidence intervals were estimated with the use of the Cox model, and the proportional hazards assumption was tested at the 0.05 significance level with the use of the Kolmogorov-type supremum test. Event rates were calculated with the use of Kaplan–Meier or cumulative incidence estimates. All analyses were conducted in accordance with the intention-to-treat principle, with data for all patients who underwent randomisation included, but to protect against bias toward non-inferiority, the analyses were repeated for the per-protocol population (all patients who underwent randomization and followed the assigned treatment regimen). Overall survival was also analysed in the subgroup of patients in the per-protocol population who had cT2c–T3 pN0 disease.

Quality-of-life end points were assessed as the change in scores between registration and randomization, and the data on the two randomized groups were compared with the use of linear mixed effects regression models. For the quality-of-life end points, a p-value of less than 0.01 was considered to indicate statistical significance, to account for multiple comparisons, and a between-group difference in mean scores of 10 points or more was considered to be clinically relevant.

Statistical Assessor’s Comment
The overall design is not standard to demonstrate the efficacy in high-risk localised or locally advanced disease. Had only non-inferiority been demonstrated, it would still not

56
have provided evidence that triptorelin (at whatever dosing regimen), would have been as
good as not using triptorelin at all as adjuvant therapy in this patient population.
Nevertheless, as the results section will show, it may be possible to draw firmer
conclusions from this study. The proposed endpoints and statistical methods to analyse
them are acceptable.

As the trial enrolled patients receiving both triptorelin and other similar products,
efficacy will need to be demonstrated in the triptorelin group alone. It may not be
necessary to demonstrate formal statistical significance in both the sub-groups, but a
similar pattern of efficacy should be observable.

2.2.3 Results:
Between April 1997 and November 2001, a total of 1113 subjects were registered into the
trial. Out of these, 970 patients underwent randomization between October 1997 and May
2002.

483 subjects were randomised to receive treatment with short-term androgen suppression,
and 487 to treatment with long-term androgen suppression.

The randomization to the trial was closed in May 2002 and after 4 years, in June 2006,
only 171 events of death had been observed. It appeared that a longer follow-up period
than the 5 years initially foreseen was likely needed, before the final analysis of the trial
results could be carried out. Furthermore, data from other trials emerged, that showed
benefit of 6 months androgen deprivation therapy (ADT) for localized disease (D’Amico)
and future trials need to be planned, for which a control arm was needed. Further, as the
trial total duration was already almost 10 years, the IDMC was consulted regarding
release of results earlier than anticipated in the protocol. The IDMC in June 2006
authorised the unplanned interim analysis. That formal interim analysis was carried out,
with the aim to stop the trial in case of evidence in favour of the null hypothesis
(inferiority) or if clear evidence for the alternative hypothesis of non-inferiority of the
experimental arm was available. That interim analysis was presented to the IDMC in
September 2006. Early stopping boundaries of the gamma family ($\gamma=-2$ for non-
inferiority and $\gamma=-4$ for futility) were defined before data analysis.

Statistical Assessor’s Comment
Although the interim analysis was not planned at the start of the study, the reason for
stopping the trial early is clear. The defining of stopping boundaries before the analysis is
key, and the proposed boundaries are appropriate. There is no evidence the trial integrity
was damaged, or would have been damaged, by the decision to perform this analysis.

2.2.3.1 Results at the Interim Analysis:
As of August 16, 2006 (at a median follow-up of 5.2 years) when the interim analysis was
conducted, 173 deaths had been reported. The stopping boundaries were a hazard ratio of
less than 0.981 for non-inferiority and of more than 1.313 for futility. The actual point
estimate of the hazard ratio was 1.43, and for this reason, the independent data monitoring
committee recommended immediate release of the interim results and publication of the
final results of testing for non-inferiority with the adjusted one-sided alpha level of
0.0429.
An alpha-spending function and a beta-spending function were built, using the Gamma family of stopping boundaries.

At the time of the interim analysis, all but 81 of the 487 patients allocated the long term androgen deprivation therapy (ADT) had completed treatment.

Three patients randomized to short term ADT received the long term ADT.

Four patients allocated the long term ADT received the short term ADT.

96 patients (19.7%) stopped the long term ADT earlier than planned by protocol. The main reasons for stopping early were refusal (39), toxicity (23) and other (21).

**Overall Survival**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short ADT (N=483)</td>
<td>Long ADT (N=487)</td>
</tr>
<tr>
<td>Death</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant disease</td>
<td>34 (20.7)</td>
<td>21 (15.0)</td>
</tr>
<tr>
<td>Infection</td>
<td>0 (0)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Second primary</td>
<td>23 (4.7)</td>
<td>19 (3.9)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>25 (5.2)</td>
<td>20 (4.1)</td>
</tr>
<tr>
<td>Other chronic disease</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Other*</td>
<td>15 (3.1)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (0.4)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

**Duration of survival (from registration)**

Randomized patients

15 Aug 2006 13:00

Number of patients at risk:

<table>
<thead>
<tr>
<th>N</th>
<th>Number of patients at risk</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>483</td>
<td>470</td>
</tr>
<tr>
<td>73</td>
<td>487</td>
<td>476</td>
</tr>
</tbody>
</table>
As shown in the tables and graph above the number of deaths were lower and the overall survival higher in the long term ADT arm.

The observed hazard ratio at the interim analysis was 1.435 which fulfilled the condition for stopping the trial early, for the reason that the short term ADT arm is significantly inferior to the long term ADT arm.

The statistical test for non inferiority was not statistically significant (P>0.1), and suggested that the results were indicative of failure to reject H0. The stopping rule was therefore applicable, so that the data could be released showing that the short term ADT arm was inferior to the long term ADT arm.

**Statistical Assessor’s Comment**

The decision to stop the trial at the interim analysis is appropriate. Clearly short-term ADT is inferior to Long-term ADT in the table and graph above.

It is a matter of clinical judgement whether this data, coupled with the known mechanism of action of triptorelin, and the results of trials of other similar GnRH therapies is sufficient to reasonably conclude that Long ADT with Triptorelin would have beaten an arm that did not include GnRH therapy, had such an arm been included in the study. Note this is identical to concluding that the short ADT arm (with Triptorelin) was not in some way detrimental to subjects, compared to not using ADT therapy at all.

**Progression-free survival**

*Clinical progression:*
### Clinical progression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short ADT</td>
<td>Long ADT</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Local progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incl. biopsy proven</td>
<td>29 (6.0)</td>
<td>8 (1.6)</td>
<td>37 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Nodal progression</td>
<td>15 (4.4)</td>
<td>2 (0.4)</td>
<td>17 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Distant progression</td>
<td>78 (16.1)</td>
<td>31 (6.4)</td>
<td>109 (11.2)</td>
<td></td>
</tr>
<tr>
<td>Site of first distant metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. bone</td>
<td>59 (73.6)</td>
<td>21 (67.7)</td>
<td>80 (73.4)</td>
<td></td>
</tr>
<tr>
<td>2. visceral</td>
<td>2 (2.6)</td>
<td>1 (3.2)</td>
<td>3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>3. lymph node outside pelvis</td>
<td>8 (10.3)</td>
<td>1 (3.2)</td>
<td>9 (8.5)</td>
<td></td>
</tr>
<tr>
<td>8. other*</td>
<td>9 (11.5)</td>
<td>8 (25.8)</td>
<td>17 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Clinical progression**</td>
<td>97 (20.1)</td>
<td>40 (8.2)</td>
<td>137 (14.1)</td>
<td></td>
</tr>
</tbody>
</table>

### Biochemical progression:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short ADT</td>
<td>Long ADT</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Biochemical progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical or biochemical progression</td>
<td>159 (32.9)</td>
<td>61 (12.5)</td>
<td>220 (22.7)</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical progression-free survival: (includes both clinical progression and death)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (N)</th>
<th>Observed Events (O) (includes clinical progression and death)</th>
<th>Hazard Ratio (98.2% CI)</th>
<th>P-Value (difference Log-Rank)</th>
<th>Clinical PFS % at 5 years (98.2% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long ADT</td>
<td>487</td>
<td>89</td>
<td>1.00</td>
<td>81.77 (76.66, 85.86)</td>
<td></td>
</tr>
<tr>
<td>Short ADT</td>
<td>483</td>
<td>155</td>
<td>1.93 (1.49,2.51)</td>
<td>&lt;0.0001</td>
<td>68.95 (63.22, 73.97)</td>
</tr>
</tbody>
</table>
Combined endpoints of PFS (clinical or biochemical progression or death)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (N)</th>
<th>Observed Events (O) (includes clinical or biochemical progression and death)</th>
<th>Hazard Ratio (98.2% CI)</th>
<th>P-Value (difference Log-Rank)</th>
<th>Combined PFS % at 5 years (98.2% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long ADT</td>
<td>487</td>
<td>106</td>
<td>1.00</td>
<td></td>
<td>78.27 (72.87, 82.72)</td>
</tr>
<tr>
<td>Short ADT</td>
<td>483</td>
<td>205</td>
<td>2.29 (1.81, 2.90)</td>
<td>&lt;0.0001</td>
<td>58.93 (52.97, 64.40)</td>
</tr>
</tbody>
</table>

As shown in the tables and graphs above, the progression free survival was better with long term androgen deprivation therapy.
Quality of Life Data
There were no significant differences between the two treatment arms. The results only showed increased fatigue for the duration of treatment, which was expected.

The long term side effects of long term ADT were as anticipated, consisting mainly of hot flushes and gynaeecomastia.

Assessor’s Comments: (Results of Interim Analysis)
The results of the interim analysis showed that the overall survival was better with long term androgen deprivation therapy compared to short term androgen deprivation. There were also statistically significant differences in the clinical progression free survival as well as the combined clinical and biochemical progression free survival, favouring treatment with long term androgen deprivation.

Therefore the overall results are in favour of long term androgen deprivation therapy as adjuvant treatment following definitive radiotherapy.

2.2.3.2 Results at the Final analysis:
The final cut-off date for data collection was September 4, 2007, with a median follow-up from the time of enrolment of 6.4 years and a total of 230 deaths. Since an interim analysis was conducted, the significance level for the final analysis was the one sided alpha level 0.0429. Analysis was carried out on an intent-to-treat basis. The analysis was also repeated in the per protocol set that includes only the eligible randomized patients who followed the allocated treatment.

The combine androgen blockade (CAB) treatment consisted in most patients of a combination of triptorelin (62.4%) or goserelin (30.1%) with bicalutamide (70.6%) or flutamide (23.5%). The irradiation is documented for 97.8% of the patients and given at a median dose of 70 Gy as recommended by the protocol. Major deviations from the recommended 6 months induction treatment were documented in 199 patients (17.9%), which consisted mostly in failure to continue the anti-androgen, adjunction of one extra injection of LH-RH or a >1 month delay between the end of the 6 months CAB and the randomization.

At the cut-off date, 4th September 2007, all but 33 of the 487 patients allocated the long term ADT had been documented to have finished treatment.

Three patients randomized to short term ADT received the long term ADT, and 3 allocated the long term ADT received the short term ADT. 112 patients (23.0%) stopped the long term ADT earlier than planned by protocol. The main reasons for stopping early were refusal, toxicity, disease progression or death.

A flow diagram of the patient enrolment and follow-up is shown below.
UKPAR Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

Figure 1. Enrollment and Follow-up of Study Patients.
CAB denotes complete androgen blockade, and RT radiotherapy.
Overall Survival

Deaths were reported in 230 patients (132 on short term ADT and 98 on long term ADT).

<table>
<thead>
<tr>
<th>Survival status</th>
<th>Short ADT (N=483)</th>
<th>Long ADT (N=487)</th>
<th>Total (N=970)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>351 (72.7%)</td>
<td>389 (79.9%)</td>
<td>740 (76.3%)</td>
</tr>
<tr>
<td>Dead</td>
<td>132 (27.3%)</td>
<td>98 (20.1%)</td>
<td>230 (23.7%)</td>
</tr>
</tbody>
</table>

The intent-to-treat analysis of the overall survival shows 82.6% survival at 5 years on the long term ADT arm and 78.8% on the short term ADT arm, with an estimated hazard ratio of 1.42 (95.71% CI: 1.09-1.85). The statistical test for non inferiority was not statistically significant (P>0.1) and confirms the results of the interim analysis. The confidence interval for the hazard ratio excludes 1, indicating that the short ADT treatment was inferior to the long term ADT treatment.

The per-protocol analysis of the overall survival confirms the results with a slightly more extreme hazard ratio of 1.47 (95.71% CI: 1.11-1.92).
UKPAR Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

**Progression-free survival**

177 patients had a clinical progression (118 on short term ADT and 59 on long term ADT) mostly in the form of distant progression (to bones; 99 vs. 48, respectively).

Biochemical progression was reported in 255 patients (184 on short term ADT and 71 on long term ADT) for a total of 281 cases with any form of disease progression (196 for short term ADT vs. 85 for long term ADT).
The clinical progression-free survival data, which includes both clinical progression and death, indicate a 5-year event free rate of 80.5% on the long term ADT arm, for 68.7% on the short term ADT arm, with a hazard ratio of 1.77.

When the data on biochemical progression was combined with the data of clinical progression, the combined progression-free survival results showed a 77.7% event free survival at 5 years on the long term ADT versus 56.8% on the short term ADT (HR=2.22).
UKPAR Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

| Short ADT | 483 | 251 | S/L: 2.20 | <0.0001 | 56.8 (52.0, 61.4) |
| Long ADT  | 487 | 143 | (1.78, 2.72) |          | 77.7 (73.5, 81.3) |

Quality of Life Data
There were no significant differences between the two treatment arms. The results only showed a increased fatigue for the duration of treatment, which was expected.

The long term side effects of long term ADT were as anticipated, consisting mainly of hot flushes and gynaecomastia.

Assessor’s Comments: (Results of Final Analysis)
The clinical progression free survival as well as the combined clinical and biochemical progression free survival, showed statistically significant differences, favouring treatment with long term androgen deprivation.

Therefore the overall results are in favour of long term androgen deprivation therapy as adjuvant treatment following definitive radiotherapy.

2.2.3.3 Results of the Subgroup Analysis:
Further subgroup analyses of the results were done in two groups according to the type of LH-RH treatment received. The first group consisted of all patients who received only Decapeptyl (Short term or Long term hormonal therapy) and the second group consisted of all other patients (who received other LHRH or a mixture of Decapeptyl and other treatment). The aim of the analyses was to assess the treatment effects in the Decapeptyl subgroup.
UKPAR Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

**Drugs and regimen used for short term CAB in patients with documented induction CAB**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Missing (N=129)</th>
<th>SADT DGP (N=298)</th>
<th>LADT DGP (N=275)</th>
<th>LADT other LHRH (N=502)</th>
<th>Total (N=1080)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Type of AA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>2 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>flutamide</td>
<td>22 (17.1)</td>
<td>69 (23.2)</td>
<td>41 (23.4)</td>
<td>52 (18.6)</td>
<td>254 (23.5)</td>
</tr>
<tr>
<td>bicalutamide</td>
<td>95 (75.2)</td>
<td>216 (73.2)</td>
<td>118 (67.4)</td>
<td>216 (78.3)</td>
<td>703 (70.6)</td>
</tr>
<tr>
<td>nilutamide</td>
<td>3 (2.3)</td>
<td>9 (3.0)</td>
<td>7 (4.0)</td>
<td>5 (1.8)</td>
<td>33 (3.1)</td>
</tr>
<tr>
<td>cyproterone acetate</td>
<td>4 (3.1)</td>
<td>2 (0.7)</td>
<td>9 (5.1)</td>
<td>3 (1.1)</td>
<td>28 (2.6)</td>
</tr>
<tr>
<td><strong>Type of LHRH-A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>2 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>goserelone</td>
<td>36 (27.9)</td>
<td>139 (79.4)</td>
<td>0 (0.0)</td>
<td>150 (74.3)</td>
<td>325 (30.1)</td>
</tr>
<tr>
<td>buserelone acetate</td>
<td>2 (1.6)</td>
<td>0 (0.0)</td>
<td>6 (3.4)</td>
<td>7 (3.5)</td>
<td>15 (1.4)</td>
</tr>
<tr>
<td>Triptorelin (=DKP)</td>
<td>79 (61.2)</td>
<td>296 (100.0)</td>
<td>0 (0.0)</td>
<td>276 (100.0)</td>
<td>672 (62.2)</td>
</tr>
<tr>
<td>leuproleine</td>
<td>8 (6.2)</td>
<td>24 (13.7)</td>
<td>0 (0.0)</td>
<td>24 (11.9)</td>
<td>56 (5.2)</td>
</tr>
<tr>
<td>other, specify</td>
<td>2 (1.6)</td>
<td>0 (0.0)</td>
<td>6 (3.4)</td>
<td>2 (1.0)</td>
<td>10 (0.9)</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>monthly depot</td>
<td>23 (17.8)</td>
<td>97 (32.6)</td>
<td>61 (34.9)</td>
<td>88 (31.9)</td>
<td>343 (31.8)</td>
</tr>
<tr>
<td>3 monthly depot</td>
<td>104 (80.6)</td>
<td>201 (67.4)</td>
<td>114 (65.1)</td>
<td>188 (68.1)</td>
<td>734 (68.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
</tr>
</tbody>
</table>

* those patients that did not have Triptorelin (Decapeptyl) for the whole duration of ADT

**Long-term ADT**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LADT DGP (N=276)</th>
<th>LADT other LHRH (N=211)</th>
<th>Total (N=487)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Type of LHRH at month 7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>0 (0.0)</td>
<td>15 (7.1)</td>
<td>15 (3.1)</td>
</tr>
<tr>
<td>goserelone</td>
<td>0 (0.0)</td>
<td>145 (68.7)</td>
<td>145 (29.8)</td>
</tr>
<tr>
<td>buserelone acetate</td>
<td>0 (0.0)</td>
<td>7 (3.3)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>triptorelin</td>
<td>276 (100.0)</td>
<td>21 (10.0)</td>
<td>297 (61.0)</td>
</tr>
<tr>
<td>leuproleine</td>
<td>0 (0.0)</td>
<td>17 (8.1)</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>other, specify</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0.0)</td>
<td>5 (2.4)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td><strong>Regimen used at month 7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>monthly depot</td>
<td>41 (14.9)</td>
<td>54 (25.6)</td>
<td>95 (19.5)</td>
</tr>
<tr>
<td>3 monthly depot</td>
<td>235 (85.1)</td>
<td>136 (64.5)</td>
<td>371 (76.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0.0)</td>
<td>21 (10.0)</td>
<td>21 (4.3)</td>
</tr>
<tr>
<td><strong>Cosing used at month 7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>3.6</td>
<td>0 (0.0)</td>
<td>37 (17.5)</td>
<td>37 (7.6)</td>
</tr>
<tr>
<td>3.7</td>
<td>5 (1.8)</td>
<td>2 (0.9)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>3.8</td>
<td>35 (12.7)</td>
<td>14 (6.6)</td>
<td>49 (10.1)</td>
</tr>
<tr>
<td>6.3</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>9.5</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>9.9</td>
<td>0 (0.0)</td>
<td>3 (1.4)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>10.2</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>10.8</td>
<td>0 (0.0)</td>
<td>106 (50.2)</td>
<td>106 (21.8)</td>
</tr>
<tr>
<td>11.2</td>
<td>3 (1.1)</td>
<td>5 (2.4)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>11.3</td>
<td>232 (64.1)</td>
<td>20 (9.5)</td>
<td>252 (51.7)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0.0)</td>
<td>21 (10.0)</td>
<td>21 (4.3)</td>
</tr>
</tbody>
</table>
UKPAR Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

**Survival Analysis - Subgroup analysis**

<table>
<thead>
<tr>
<th>Treatment subgroup</th>
<th>Patients (N)</th>
<th>Observed Events (O)</th>
<th>Hazard Ratio (95.71% CI)</th>
<th>1-sided P-value for non-inferiority</th>
<th>2-sided P-value for difference (Log-Rank)</th>
<th>% at 5 Year(s) (95.71% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERALL SURVIVAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triptorelin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short ADT</td>
<td>298</td>
<td>73</td>
<td>S/L: 1.28 (0.89, 1.84)</td>
<td>0.3786</td>
<td>0.0880</td>
<td>83.5 (78.5, 87.4)</td>
</tr>
<tr>
<td>Long ADT</td>
<td>276</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td>84.6 (79.5, 88.5)</td>
</tr>
<tr>
<td>Other GnRHS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short ADT</td>
<td>185</td>
<td>59</td>
<td>S/L: 1.66 (1.11, 2.47)</td>
<td>0.8486</td>
<td>0.0055</td>
<td>76.6 (69.2, 82.6)</td>
</tr>
<tr>
<td>Long ADT</td>
<td>211</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
<td>85.1 (79.1, 89.6)</td>
</tr>
<tr>
<td>CLINICAL PROGRESSION-FREE SURVIVAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short ADT</td>
<td>298</td>
<td>113</td>
<td>S/L: 1.71 (1.25, 2.34)</td>
<td>0.0004</td>
<td></td>
<td>69.9 (64.1, 75.0)</td>
</tr>
<tr>
<td>Long ADT</td>
<td>276</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td>79.4 (73.8, 83.9)</td>
</tr>
<tr>
<td>Other GnRHS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short ADT</td>
<td>185</td>
<td>78</td>
<td>S/L: 1.86 (1.30, 2.66)</td>
<td>0.0003</td>
<td></td>
<td>66.4 (58.5, 73.2)</td>
</tr>
<tr>
<td>Long ADT</td>
<td>211</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
<td>82.1 (75.8, 87.0)</td>
</tr>
<tr>
<td>CLINICAL/BIOLOGICAL PROGRESSION-FREE SURVIVAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short ADT</td>
<td>298</td>
<td>153</td>
<td>S/L: 2.29 (1.72, 3.05)</td>
<td>&lt;0.0001</td>
<td></td>
<td>57.4 (51.2, 63.0)</td>
</tr>
<tr>
<td>Long ADT</td>
<td>276</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td>77.1 (71.4, 81.9)</td>
</tr>
<tr>
<td>Other GnRHS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short ADT</td>
<td>185</td>
<td>98</td>
<td>S/L: 2.07 (1.50, 2.86)</td>
<td>&lt;0.0001</td>
<td></td>
<td>55.8 (47.8, 63.2)</td>
</tr>
<tr>
<td>Long ADT</td>
<td>211</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
<td>78.5 (71.7, 83.8)</td>
</tr>
</tbody>
</table>

Cl: confidence interval, ADT: Androgen deprivation therapy  
* P-value for non-inferiority (primary endpoint)  
* b: P-value for difference (log-rank)  
* Combined events including death  
* Hazard ratios and tests are calculated discounting the registration period to avoid non-proportional hazards  
Source: EORTC 22961 Subgroup Analysis Report

**Duration of survival (from registration)**

- **Randomized patients (DKP only)**

- **Number of patients at risk**
  - 73 298 285 254 130 17 19 12 10 8 6 4 2 0
  - Number of patients at risk: 73
  - Treatment: Short ADT
  - Treatment: Long ADT

<table>
<thead>
<tr>
<th>Treatment Group DKP</th>
<th>Patients (N)</th>
<th>Observed Events (O)</th>
<th>Hazard Ratio (95.71% CI)</th>
<th>1-sided P-value for non-inferiority</th>
<th>2-sided P-value for difference (Log-Rank)</th>
<th>% at 5 Year(s) (95.71% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short ADT</td>
<td>298</td>
<td>73</td>
<td>S/L: 1.28 (0.89, 1.84)</td>
<td>0.3786</td>
<td>0.0880</td>
<td>83.5 (78.5, 87.4)</td>
</tr>
<tr>
<td>Long ADT</td>
<td>276</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td>84.5 (79.5, 88.5)</td>
</tr>
</tbody>
</table>
In the subgroup of patients with other LHRH, deaths were reported in 104 patients (59 on short term ADT and 45 on long term ADT).

The intent-to-treat analysis of the overall survival shows 76.6% survival at 5 years on the short term ADT arm and 85.1% on the long term ADT arm, with an estimated hazard ratio of 1.66 (95.71% CI: 1.11-2.47). The statistical test for non inferiority is clearly not statistically significant (P>0.1) but in this group, the statistical test for difference is statistically significant, indicating that the short ADT treatment is significantly inferior to the long ADT treatment.
The per-protocol analysis of the overall survival shows 77.4% survival at 5 years on the short term ADT arm and 85.5% on the long term ADT arm, with an estimated hazard ratio of 1.73 (95.71% CI: 1.14-2.63). The statistical test for non inferiority is clearly not statistically significant (P>0.1) but in this group, the statistical test for difference is statistically significant, indicating that the short ADT treatment is significantly inferior to the long ADT treatment.

However, the forest plot which represents graphically the heterogeneity of treatment effects between the two subgroups, doesn’t show a significant difference of treatment effects between the two groups (heterogeneity test, p>0.1).
**Overall Survival - Subgroup Comparison**

In the Decapeptyl subgroup, 105 patients have had a clinical progression (73 on short term ADT and 32 on long term ADT).

Biochemical progression was reported in 154 patients (118 on short term ADT and 36 on long term ADT) for a total of 168 patients with some form of disease progression (125 vs. 43).

The clinical progression-free survival data indicate a 5-year event free rate of 79.4% on the long term ADT arm, for 69.9% on the short term ADT arm, with a hazard ratio of 1.71 that indicates a significantly shorter clinical progression-free survival with short term ADT.

The biochemical progression-free survival data point in the same direction with 77.1% event free survival at 5 years on the long term ADT versus 57.4% on the short term ADT (HR=2.29).

Considering only the cumulative incidence of events of clinical progression or death due to prostate cancer, it appears that it amounts to 16.0% at 5 years on the short term ADT arm and 5.9% on the long term ADT arm.

In the subgroup of patients with other LHRH, results are very similar to the Decapeptyl subgroup and in the same direction.

The forest plot did not show a significant difference of treatment effects between the two groups (heterogeneity test, p>0.1).
Clinical Progression-Free Survival - Subgroup Comparison

The subgroup analysis shows similar treatment effects between the two subgroups. The number of events planned for the final analysis was 285 (after interim analysis) and in each subgroup the number of events observed is under 130. Therefore, there is a lack of power to show a significant result for the primary endpoint especially in the Decapeptyl subgroup.

Statistical Assessor’s Comment
The results for triptorelin compared to other GnRHs are broadly similar – however the point estimate for the hazard ratio for overall survival is much smaller for triptorelin than for the other GnRHs. It is a matter of clinical judgement whether this is important. Although statistical significance has not been demonstrated, the trial would not have been powered to detect this.

Evaluation
Initial Reference Studies
The submitted reference studies (EORTC 22863, RTOG 85-31, RTOG 86-10, and RTOG 92-02) have all been done with the use of Goserelin 3.6 mg formulation (Zoladex).

The RTOG 85-31 trial demonstrated the benefit of immediate adjuvant use of goserelin, rather than reserving for treatment of relapse after radiotherapy, in patients with locally advanced prostate cancer with Gleason scores \(\geq 7\), with improvements in survival, local failure rate and rates of distant metastases.

The EORTC 22863 study showed that addition of 3 years of Zoladex 3.6 mg 4 weekly, following definitive radiotherapy, improved the overall survival and progression free survival in locally advanced prostate cancer, and patients with Grade 3 localised prostate cancer. A sub-group analyses based on Gleason score was not evident and hence a complete correlation with the RTOG 85-31 results is not possible.

The RTOG 86-10 study demonstrated the benefit of better disease control, with the use of Goserelein prior to and concomitantly with external beam radiotherapy in patients with locally advanced prostate cancer with a Gleason score of 2-6. There was no statistically significant benefit in patients with a Gleason score 7-10, in terms of better disease control.
Considering the above three trials together, it is evident that the use of neoadjuvant, concomitant and adjuvant goserelin with radiotherapy in locally advanced prostate cancer is clearly beneficial. The other two trials (RTOG 92-02, and the pivotal study for these applications- EORTC 22961) discussed, which were conducted subsequent to the above three trials, were designed with neoadjuvant and concomitant androgen deprivation as standard. However, the optimum duration of adjuvant therapy; and specifically in different sub-groups of patients, based on risk factors especially Gleason’s scores, was not fully clear. The subsequent two trials have attempted to address the issue regarding optimum duration of adjuvant therapy. The RTOG trials have analysed benefits in patient subgroups based on Gleason’s scores, but similar analyses are not available in the EORTC trials.

The later RTOG trial 92-02 demonstrated improvement in disease control with the use of long term goserelin with radiotherapy over the use of short term goserelin with radiotherapy. However, a statistically significant beneficial effect on overall survival with the use of long term goserelin was only seen in patients with prostate cancer with high Gleason scores of 8-10. In the discussion in the publication of the 10 year follow-up data of the trial (ref: Horwitz EM et al, 2008; JCO), the investigators list several possible reasons for the lack of a statistically significant overall survival difference in the patients with Gleason scores of 7 or lower. One reason stated may be that the follow-up was not long enough to detect a statistically significant benefit in patients with the low Gleason scores.

Therefore, considering all the trials together, there is a benefit of neoadjuvant, concomitant use and long term adjuvant use of goserelin, with definitive radiotherapy in patients with locally advanced or high risk localised prostate cancer, at least in terms of better disease control. From the follow-up data available in the submitted studies, a benefit in overall survival is evident for patients with Gleason scores 8-10. The benefit in overall survival for patients with Gleason score ≤7 is not evident at present, as the follow-up in the studies have not been long enough to demonstrate a statistically significant benefit in this group.

These studies have supported the following indications in the Zoladex 3.6 mg and 10.8 mg SmPC in the UK:

- As adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer where Zoladex has demonstrated improved disease-free survival and overall survival.
- As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer where Zoladex has demonstrated improved disease-free survival.

**Goserelin effect vs. LHRH/ androgen deprivation effect**

The results of the trials conducted with goserelin have been referred to in several clinical guidelines, and the data interpreted to conclude a benefit of adjuvant androgen deprivation therapy with radiotherapy in patients with locally advanced or high-risk localised disease.

The NICE guidelines on prostate cancer states, “Several randomised trials (Kumar et al. 2006) have shown that adjuvant androgen withdrawal improves overall survival in men receiving radical radiotherapy. Sub-group analysis suggests that the survival benefit of
adjuvant hormonal therapy is greatest in men with high grade disease. Most of the evidence relates to goserelin given for three years or more, but a single randomised trial (Tyrrell et al. 2005) suggests the survival benefit of adjuvant bicalutamide monotherapy is comparable.”

The NCCN practice guidelines in Oncology refer to androgen deprivation therapy with LHRH agonists (medical castration) and do not specify any particular LHRH agonist. This guideline recommends radiotherapy with neoadjuvant, concomitant and long term adjuvant androgen deprivation therapy (2-3 years) in the treatment of locally advanced disease, as well in the treatment of disease with high risk of recurrence (T3a, or Gleason score 8-10, or PSA >20 ng/mL).

The submitted pivotal trial (EORTC 22961) also infers an effect of LHRH agonists in general from results of previous goserelin based trials. Treatments on this trial have included triptorelin (>60%), goserelin (approximately 30%), leuprorelin, and buserelin.

The mechanism of action of LHRH agonists has been accepted as the suppression of testosterone to castrate levels.

Therefore, current clinical guidelines and practice do not differentiate between the different LHRH agonists for the purposes of androgen deprivation therapy.

In 2008, a review of indications was requested for LHRH agonists, which included Zoladex (Goserelin), Prostap (Leuprorelin), Decapeptyl, and Suprefact (Buserelin). This was triggered by a complaint to the Prescription Medicine Code of Practice Authority (PMPCA), with the issue being confusion regarding the licensed indication for Decapeptyl in “advanced prostate cancer” as to whether this indicated metastatic or locally advanced disease. This led to the respective MAHs submitting variation applications for better specification of indications, with submission of supportive data. The indication for use as “adjuvant to radiotherapy in locally advanced and high-risk localised disease” was added to the Zoladex and Prostap SmPC. The large bulk of data in support of this indication was from studies conducted with goserelin. There was a study conducted with the use of leuprorelin (n=88) or goserelin (n=10) which compared 3D conformal radiotherapy alone versus combined 3D-CRT with 6 months of androgen suppression therapy. This study along with data from studies with goserelin was used to support the adjuvant treatment indication for Prostap, following radiotherapy. The currently submitted pivotal study is a much larger study conducted with 970 patients, >60% of whom received triptorelin as the androgen suppression therapy.

Data to support Triptorelin
The only trial discussed in the dossier and conducted using triptorelin, is the EORTC 22961 trial which is submitted as the pivotal study to support these applications. The trial design infers that the benefit of neoadjuvant, concomitant and adjuvant androgen deprivation therapy, seen with goserelin, is applicable to all LHRH agonists.

The EORTC 22961 trial showed that short ADT with LHRH agonists were inferior to long term ADT with LHRH agonists following definitive radiotherapy and hormonal therapy as described above. Subgroup analyses of the results to evaluate the effects of triptorelin (Decapeptyl) show the results to be fairly consistent and similar between Decapeptyl and other LHRH agonists (majority of whom were treated with goserelin).
From the results it is concluded that long term adjuvant treatment with Decapeptyl SR is beneficial over short term treatment following definitive radiotherapy. These effects are similar for both Decapeptyl and other LHRH agonists (a large proportion of which was goserelin) used in the study.

As stated in the statistical assessment above, it is a matter of clinical judgement whether this data, coupled with the known mechanism of action of triptorelin, and the results of trials of other similar GnRH therapies is sufficient to reasonably conclude that Long ADT with triptorelin would have beaten an arm that did not include GnRH therapy, had such an arm been included in the study. This is identical to concluding that the short ADT arm (with triptorelin) was not in some way detrimental to subjects, compared to not using ADT therapy at all. The applicant has provided a brief comparison of efficacy results between the pivotal study and the reference studies; and this comparison is useful in addressing the above issue. The similar efficacy between triptorelin and other LHRH agonists (mainly goserelin) has been shown in the pivotal study, for use in long term androgen deprivation following radiotherapy. The efficacy for triptorelin as adjuvant treatment in general following radiotherapy, could be supported by comparing the efficacy of results of goserelin in the pivotal study with the goserelin efficacy results in the reference studies.

The applicant’s discussion to compare the efficacy results of all studies is provided in module 2.7.3-Summary of Clinical Efficacy. A direct comparison of results between Study EORTC 22961 and the four reference studies is not possible due to the different designs and/or endpoints.

- In the pivotal EORTC 22961 trial, the 5-year overall survival rate [95.71% CI] was 81.0% [77.0; 84.5] in the short ADT group and 84.8% [81.1; 87.9] in the long ADT group.
- The RTOG-92-02 trial, conducted using goserelin, also compared the long term and short term androgen deprivation therapy, as adjuvant to radiotherapy, and this trial showed a statistically significant improvement on overall survival with long term androgen deprivation in a subgroup of patients with Gleason score of 8 to 10: 5-year OS rate of 81.0% versus 70.7% (p = 0.044).
- A further useful comparison is with the results of the EORTC 22863 trial, which was also conducted with the use of goserelin. The results showed that 3 years of androgen deprivation therapy significantly improved 5-year overall survival rate compared with radiotherapy alone (78% (95% CI [72; 84]) versus 62% [52; 72] (p = 0.0002)).

The three trials show an overall survival between 70 and 84 % with the use of adjuvant androgen deprivation therapy. Differences between short term and long term ADT have been shown by the EORTC 22961 and the RTOG 92-02 trials. The overall survival with both durations of therapy is greater than the 5 year median overall survival of 62% seen in the EORTC 22863 trial with the use of radiotherapy alone. Therefore these results of the early reference studies show a consistent and similar benefit of adjuvant LHRH agonist therapy with goserelin, following radiotherapy. Since the effects are seen to be similar between triptorelin and goserelin, in the pivotal study, this supports the conclusion that the beneficial effects of adjuvant therapy in general, following radiotherapy is applicable to triptorelin as well.
As stated previously the high risk factor of a Gleason score 8-10 was not a criteria for inclusion for patients with localised disease, in the EORTC 22961 trial. The population included in the pivotal trial does not appear to include a patient population that could be classified as high-risk localised disease. An expert statement has been provided, written by a leading expert in prostate cancer and the principle investigator for the EORTC 22961 trial. The statement refers to the use of triptorelin use based on the results of the EORTC 22961 trial. The statement recommends the use of triptorelin as concomitant and adjuvant treatment with radiotherapy, in patients with locally advanced prostate cancer. There is no recommendation regarding patients with high-risk localised disease.

Written advice was sought by the assessors, from a clinical expert in prostate cancer regarding differences between the locally advanced and high-risk localised disease prostate cancer; and also regarding inclusion of patients with regional lymph nodal metastases in the pivotal study. These issues were further discussed at the Commission of Human Medicines meeting (April 2011). The clinical expert was of the opinion that the patients with regional lymph nodal metastases, should be included under the locally advanced disease category; as lymph nodal metastases may be detectable by pathological staging in patients staged as N0 by radiological imaging. In clinical practice patients with regional lymph nodal metastases who are suitable for radical/definitive radiotherapy would be treated with radiotherapy and androgen deprivation therapy in the same way as locally advanced disease without clinically detected lymph nodal metastases. In addition the distinction between the locally advanced disease and high-risk localised disease is highly dependant on the thoroughness of staging modalities used. Hence the patients classed as high-risk localised disease may have locally advanced disease which is not detectable by the available clinically staging modalities. The NICE guidelines state that high-risk localised disease should be treated in the same way as locally advanced disease.

Therefore in clinical practice there is likelihood of overlap between the high-risk localised disease, locally advanced disease, and disease with regional lymph nodal metastases. There is also no clear definition regarding these disease groups. The population for which the proposed indication is intended would be patients that are considered suitable for definitive/ radical radiotherapy; and could include any of the three groups described above. Therefore the evidence provided was considered sufficient to support the proposed indication in the locally advanced and high-risk localised disease groups.

The proposed indication has been approved for the 3 mg and 11.25 mg strengths of Decapeptyl. The 6-monthly injection Decapeptyl SR 22.5 mg has the benefit of longer time between injections. There are no new safety concerns with the proposed indication.

Decision – Granted 24/11/2011
Annex 2

Reference(s): PL 34926/00013 - 0014

Product(s): Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

Marketing Authorisation Holder: Ipsen Limited

Active Ingredient(s): Triptorelin Pamoate

Reason
To update SmPC in order to further define the target patient population and align with current clinical practice and uro-oncology clinical guidelines.

Supporting Evidence
Clinical studies: neoadjuvant treatment prior to radiotherapy

The MAH refers to clinical data from 10 published papers, corresponding to 8 clinical studies, in support of the proposed indication:
- As neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

Neoadjuvant (radiotherapy) studies of triptorelin
Two published studies of triptorelin are submitted in support:


Design
Prospective single arm European study to investigate change in prostate volume after 2 months of neoadjuvant triptorelin therapy.

Patient population
28 patients, average age 68.25 years, with localised histologically-confirmed prostate adenocarcinoma, were referred for conformal 3D radical radiotherapy in 2002-2003. High risk patients were defined as: T3 or Gleason score > 7 or PSA >20 ng/dL. All patients were N0 M0 based on radiographic assessment. 19 patients (68%) were high risk.

Treatment
Triptorelin 11.25 mg (every 3 months) intramuscularly in combination with flutamide 250 mg TID as neoadjuvant treatment for 2 months prior to radiotherapy. Low risk patients received no further hormone treatment. Medium risk patients were treated until the end of radiotherapy. High risk patients were treated for 2 years.

Endpoints
Prostate volume was calculated prior to, and after 2 months of, neoadjuvant hormone therapy. Based on transrectal ultrasound. Other endpoints included planning volume, based on transrectal ultrasound and simulation CT, and radiation dose.
Results
The mean prostate volume prior to neoadjuvant therapy was 50.65 cm², decreasing to 38.97 cm² after 2 months of therapy (p<0.001), a 24% reduction. There were statistically significant reductions in planning volumes, and in radiation doses administered. After an average follow-up of 26 months, 3-year overall survival and disease-free survival were 100% and 81.45% respectively.

Assessor’s comment:
There does not appear to have been a blinded independent evaluation of prostate or planning volumes. The authors’ definition of high risk includes patients with Gleason score 7: this is considered intermediate in guidelines such as NICE. However, this study provides evidence that neoadjuvant treatment with triptorelin in combination with an anti-androgen is associated with a reduction in prostate volume and radiotherapy planning volumes in high risk localised prostate cancer. However, a benefit in terms of disease progression or survival cannot be concluded from this study.
Ozyigit et al 2003: Administration Of Curative Radiotherapy In Combination With Hormone Therapy in Localized Adenocarcinoma of Prostate Cases

**Design**
Prospective single arm study to investigate change in prostate volume after 3 months of neoadjuvant triptorelin therapy.

**Patient population**
50 patients with histologically-confirmed prostate cancer, stage T1-T3b, N0M0 were categorised as low or high risk according to clinical staging, Gleason score and PSA level. 40 patients were high risk, defined as stage T2b-T3b N0M0 or Gleason score ≥ 7 or PSA ≥ 10ng/ml. Median age was 68 years.

**Treatment**
47 patients received triptorelin acetate (Decapeptyl) as deep intramuscular injection every 28 days in combination with cyproterone acetate intramuscularly every 2 weeks. 3 patients received goserelin acetate instead of triptorelin. Treatment was neoadjuvant for 12 weeks. High risk patients received a further 24 weeks of adjuvant hormone treatment.

**Endpoints**
These included prostate volume measured by transrectal ultrasound scan, PSA levels.

**Results**
Prostate volume as measured using transrectal ultrasound was 15-105 mL (median 38 mL) before neoadjuvant hormone treatment, and 14.5-65 mL (median 28 mL) before radiotherapy. This reduction was found to be statistically significant (p<0.001). The authors also reported that PSA levels before radiotherapy were significantly lower than pre-biopsy (median 1.05ng/mL vs. 15 ng/ml p<0.001).

**Assessor’s comment:**
There does not appear to have been a blinded independent evaluation of prostate or planning volumes. The authors’ definition of high risk equates to the NICE guideline high and intermediate risk criteria. 44% of patients were T3 and, therefore, would be classified according to current guidelines as locally invasive disease. This study provides evidence that neoadjuvant treatment with triptorelin in combination with an anti-androgen is associated with a reduction in prostate volume and PSA in high risk localised and locally advanced prostate cancer. However, a benefit in terms of disease progression or survival cannot be concluded from this study.

**Neoadjuvant (radiotherapy) studies of other GnRH analogues**
Pilepich et al 2001: Phase III Radiation Therapy Oncology Group (RTOG) Trial 86-10 of Androgen Depravation Adjunct to Definitive Radiotherapy in Locally Advanced Carcinoma of the Prostate

Roach et al 2008: Short-Term Neoadjuvant Androgen Deprivation Therapy and External-Beam Radiotherapy for Locally Advanced Prostate Cancer: Long-Term Results of RTOG 8610

**Design**
This was a randomised controlled trial to investigate the benefit of neoadjuvant androgen deprivation therapy (ADT) in patients with prostate cancer undergoing radiotherapy.
Patient population
Between 1987 and 1991, 456 patients (median age 70) were randomised. Clinical stage was T2-T4 bulky tumours (product of palpable tumour dimension of 25cm² or more on digital rectal examination), with or without pelvic lymph node involvement.

Treatment
After stratification by stage and grade, patients were randomised 1:1 to external beam radiotherapy alone, or in combination with goserelin 3.6mg every 4 weeks and flutamide 250 mg TID, for 2 months before, and during radiotherapy. Total treatment duration was 112 days.

Endpoints
The primary endpoint was stated as locoregional control. Secondary endpoints included disease-free survival (DFS) and overall survival (OS).

Results
Pre-treatment prognostic factors were well-balanced between arms. The long-term results were reported by Roach et al (2008). Ten-year overall survival estimates (43% vs 34%, HR 1.18, 95% CI 0.96 to 1.46) and median survival times (8.7 vs 7.3 years) favoured the ADT arm but did not reach statistical significance (p=0.12). ADT was associated with a statistically significant improvement in 10-year disease-specific mortality (23% vs 36%; p=0.01), distant metastases (35% vs 47%; p=0.006), DFS (11% v 3%; HR 1.91, 95% CI 1.58-2.32), and biochemical failure (65% v 80%; p<0.0001). There was no significant difference in the local progression rate between arms at 10 years. At 10 years, fatal cardiac events had occurred in 12.5% of the ADT arm, compared with 9.1% treated with RT alone (p=0.32).

Assessor’s comment:
This was first Phase III RCT to investigate neoadjuvant ADT in combination with radiotherapy in men with locally-advanced prostate cancer. The study appears to be unblinded. It is unknown whether progression was independently adjudicated. Although 30% had stage T2b or T2c, tumours were bulky. Therefore relevance to a high-risk localised prostate cancer population may be limited.

The RTOG 86-10 study showed an improvement in disease control, as well as the duration of disease control, on addition of ADT prior to and concomitantly with external beam radiotherapy. The only GnRH analogue used in this study was goserelin. There was no statistically significant difference in the overall survival.

Denham et al 2005: Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial

Denham et al 2011: Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial

Design
This was an open-label randomised controlled study to investigate the benefit of neoadjuvant ADT prior to and during radiotherapy, compared to radiotherapy alone, in the treatment of prostate cancer.
Patient population
Between 1996 and 2000, 818 patients with locally-advanced prostate cancer, mean age 68 years, were randomised. Staging was T2b-T4, N0,M0.

Treatment
Patients were stratified by age, stage, tumour differentiation, initial PSA, and were randomly assigned 1:1:1 to radiotherapy alone, 3 months of ADT (3.6 mg goserelin given monthly sc with 250 mg flutamide orally TID) starting 2 months before radiotherapy or 6 months’ androgen deprivation, with the same regimen, starting 5 months before radiotherapy.

Endpoints
Primary endpoints were all-cause mortality and prostate cancer specific survival. Secondary endpoints included PSA progression, local progression, distant progression, secondary therapeutic intervention, event-free survival (time to first PSA or clinical progression, secondary therapeutic intervention or death). All relapse and mortality data were reviewed before data close-out in August 2010 by a masked endpoints committee.

Results
The 10 year results were reported by Denham et al 2011. Compared with radiotherapy alone, the following benefits were demonstrated for both 3 and 6 months of neoadjuvant ADT:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>3 months ADT HR (95% CI)</th>
<th>6 months ADT HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA progression</td>
<td>0.72 (0.57-0.90)</td>
<td>0.57 (0.46-0.72)</td>
</tr>
<tr>
<td>Local progression</td>
<td>0.49 (0.33-0.73)</td>
<td>0.45 (0.30-0.66)</td>
</tr>
<tr>
<td>Event-free survival</td>
<td>0.63 (0.52-0.77)</td>
<td>0.51 (0.42-0.61)</td>
</tr>
<tr>
<td>Distant progression</td>
<td>0.89 (0.60-1.31)</td>
<td>0.49 (0.31-0.76)</td>
</tr>
<tr>
<td>Prostate cancer specific mortality</td>
<td>0.86 (0.60-1.23)</td>
<td>0.49 (0.32-0.74)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.84 (0.65-1.08)</td>
<td>0.63 (0.48-0.83)</td>
</tr>
</tbody>
</table>

Assessor’s comment
The results demonstrate a clear benefit for a neoadjuvant GnRH analogue (goserelin) + anti-androgen prior to radiotherapy, in localised and locally-advanced prostate cancer. 6 months of treatment is more beneficial than 3 months. The radiation dose was lower than that commonly used in current practice (66 Gy vs. 74 Gy).

Although it is not possible to calculate the proportion with high-risk localised disease, from the data provided, it is likely that cases were included, given the range of stage, Gleason scores and PSA levels in the baseline population.

Jones et al 2011: Radiotherapy and short-term androgen deprivation for localised prostate cancer (RTOG 94-08)

Design
This was a randomised controlled study to investigate the benefit of neoadjuvant ADT prior to radiotherapy, compared to radiotherapy alone.
**Study population**
Between 1994 and 2001, 1979 patients with stage T1b-T2b prostate adenocarcinoma and PSA ≤ 20ng/mL were randomised. Median age was 70 years.

**Treatments**
Randomisation was 1:1 to radiotherapy alone, or combined with 4 months of ADT, starting 2 months prior to radiotherapy. ADT consisted of flutamide 250mg TID with either goserelin 3.6 mg monthly subcutaneously or leuprorelin 7.5 mg monthly intramuscularly.

**Endpoints**
The primary endpoint was overall survival. Secondary endpoints included disease-specific mortality, distant metastases, biochemical failure and rate of positive findings on repeat prostate biopsy at 2 years.

**Results**
The 10-year overall survival was 62% for radiotherapy +ADT compared to 57% for radiotherapy alone (HR for death with RT alone 1.17; 95% CI 1.01-1.35).

ADT was associated with reduced disease-specific mortality (8% vs. 4%, HR 1.87; 95% CI 1.27-2.74). ADT was also associated with significant improvements in biochemical failure, distant metastases, and positive findings at 2 year repeat prostate biopsy.

The 10 year cumulative incidence of death from causes other than prostate cancer was 34% in the radiotherapy + ADT group, compared to 37% for radiotherapy alone. Patient-reported erectile dysfunction was measured using the Sexual Adjustment Questionnaire. The proportion reporting ‘when sexually excited, always or almost always able to have an erection’ was 21% after 1 year compared to 48% at baseline in the ADT arm. In the radiotherapy only arm, the respective proportions were 31% and 54%. Temporary acute hepatic toxic effects were observed more commonly in the ADT group.

**Assessor’s comment:**
This study provides evidence of the benefit of neoadjuvant GnRH analogue + anti-androgen, prior to radiotherapy, in terms of overall survival, and disease-specific endpoints. As would be expected, short-term treatment does not appear to be associated with long-term safety concerns. However it is notable that there is some evidence of a detrimental affect on sexual function at 1 year.

The study population was lower risk than the target population for the proposed neoadjuvant indication: only 9% had Gleason score 8-10. The radiation dose was lower than that commonly used in current practice (66.6 Gy vs. 74 Gy).

Laverdiere et al 2004: The efficacy and sequencing of a short course of androgen suppression on freedom from biochemical failure when administered with radiation therapy for T2-T3 prostate cancer

**Design**
Randomised controlled study to compare benefit of radiotherapy alone, and in conjunction with androgen deprivation therapy (ADT).

**Patient population**
In 1990-1999, 161 patients with stage T2-T3 prostate cancer were randomised. Median age was 69 years. 70% were stage T2.

Treatments
Patients were randomised to radiotherapy alone, radiotherapy preceded by 3 months of GnRH analogue + anti-androgen, or radiotherapy in conjunction with 10 months of GnRH analogue + anti-androgen (3 months neoadjuvant). The Radiotherapy was external beam with a total dose of 64G. Details of ADT were not specified.

Endpoints
The primary endpoint was clinical or biochemical disease-free survival.

Results
7-year biochemical-free survival rates were 42%, 66% and 69% in the radiotherapy only, radiotherapy + 3 months ADT, and radiotherapy + 10 months ADT arms, respectively. These differences were statistically significant for both ADT groups compared to radiotherapy only.

Assessor’s comment:
This study demonstrates a benefit for neoadjuvant GnRH analogue + anti-androgen, compared to radiotherapy alone, as measured by biochemical-free survival rates. The adjuvant component does not appear to confer an additional benefit. The ability to extrapolate the results is limited as insufficient detail is included regarding risk criteria and treatments administered.

D’Amico et al 2004: 6-Month Androgen Suppression Plus Radiation Therapy vs Radiation Therapy Alone for Patients With Clinically Localized Prostate Cancer: A Randomized Controlled Trial

Design
This was an open-label randomised controlled study to assess the benefit of neoadjuvant/concomitant ADT in conjunction with radiotherapy, compared to radiotherapy alone.

Patient population
Between 1995 and 2001, 206 patients (median age 72.5 years) with clinically localised prostate cancer (T1b-T2b, NX, M0) were randomised. To be eligible, patients had a PSA >10 ng/mL, a Gleason score of at least 7, or radiographic evidence of extraprostatic disease.

Treatments
Patients were randomised 1:1 to receive 70Gy 3-D conformal radiation therapy either alone or in combination with 6 months of androgen deprivation therapy (ADT), including 2 months prior to radiotherapy. Leuprolelin 7.5 mg im monthly, leuprolelin 22.5 mg im every 3 months, goserelin 3.6 mg sc monthly or goserelin10.8 mg sc every 3 months was administered with flutamide 250 mg TID.

Endpoints
Main outcome measures were time to PSA failure (PSA > 1.0 ng/mL and increasing > 0.2 ng/mL on consecutive visits), and overall survival.
Results
There was an increase in 5-year overall survival in patients receiving neoadjuvant/concomitant ADT: 88% vs. 78% (adjusted HR for overall mortality 2.04; 95% CI 1.01-4.20). There were also statistically significant improvements in PSA failure, survival free of salvage AST and prostate cancer specific mortality. There was no evidence of increased cardiovascular deaths in the AST arm. Patients receiving RT + AST showed increased incidence of gynaecomastia and impotence.

Assessor’s comment
This study demonstrates clinically relevant benefits for neoadjuvant / concomitant GnRH analogue + anti-androgen compared to radiotherapy alone. Localised and locally advanced prostate cancer patients were included.

D’Amico et al 2008: Risk of Prostate Cancer Recurrence in Men Treated With Radiation Alone or in Conjunction With Combined or Less Than Combined Androgen Suppression Therapy
This paper reports a post-hoc analysis of data from D’Amico et al 2004 (see above) to investigate the association between actual months of anti-androgen use and risk of recurrence. After a median follow-up of 8.2 years, an increased risk of PSA recurrence was associated with Gleason score 8-10 and stage T2 disease. Recurrence risk was decreased with each additional month of anti-androgen use after adjustment for known prognostic factors and factors that could cause LFT elevation and therefore increase likelihood of flutamide discontinuation.

Assessor’s comment:
The authors acknowledge that this analysis was hypothesis-generating. However it dose raise the question of whether neoadjuvant treatment with gonadorelin analogues, in the absence of anti-androgen treatment, is beneficial.

Clinical studies: adjuvant treatment after radical prostatectomy
The MAH refers to clinical data from 8 published papers, corresponding to 7 clinical studies in support of the proposed indication:
- As adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.

None of the studies investigate triptorelin.

Messing et al 1999: Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer (ECOG 7887)

Messing et al 2006: Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy.

Design
This randomised controlled open-label study was designed to investigate the benefit of adjuvant androgen deprivation therapy following radical prostatectomy, compared to observation alone.

Study population
Between 1988 and 1993, 98 men who underwent radical prostatectomy and pelvic lymphadenopathy for clinically stage T1b-T2 prostate cancer, and who were found to have nodal metastases (but were otherwise disease-free post-operatively) were randomised. Median age was 65.6 years.

**Treatment**
Patients were randomly assigned to immediate androgen deprivation therapy (goserelin 3.6 mg sc monthly or bilateral orchidectomy) or observation only.

**Endpoints**
The primary endpoint was progression-free survival; secondary endpoints were overall and disease-specific survival.

**Results**
Of the patients assigned immediate ADT, 13 underwent bilateral orchidectomy and 33 received continual goserelin. 10 year follow-up data was reported by Messing et al 2006: At median follow-up of 11.9 years, men assigned immediate ADT had a significant improvement in overall survival (hazard ratio 1.84 95% CI 1.01–3.35, p=0.04), prostate-cancer-specific survival (4.09 95% CI 1.76–9.49, p=0.0004), and progression-free survival (3.42 95% CI 1.96–5.98, p<0.001). Median overall survival was 13.9 years in the immediate ADT group, compared to 11.3 years in the observation group. The authors state that apart from side-effects such as hot flushes, ADT was generally well-tolerated, and there were no discontinuations due to toxic effects. However bone density related events were not specifically monitored at that time. There were no reports of osteoporotic fracture. There was no evidence of an increase in cardiovascular deaths in the immediate ADT group.
UKPAR Decapeptyl SR 22.5mg Powder and Solvent for Suspension for Injection

**Assessor’s comment:**

The results appear to demonstrate a clear benefit for long-term adjuvant treatment with GnRH analogue or bilateral orchidectomy, in patients undergoing radical prostatectomy for localised prostate cancer who were subsequently found to have nodal disease. This population could be considered to be consistent with the target population for the proposed indication: locally advanced prostate cancer at high risk of disease progression.
In this relatively old study, PSA levels were not used in the decision to initiate treatment in the observation arm. Therefore the results may not be fully generalisable to current clinical practice.

The study has been criticised due to small sample size, and the increased likelihood of imbalance between treatment groups. After adjusting for Gleason scores following a retrospective central pathology review of about 50% of the original histological slides, associations between allocated treatment and survival were still statistically significant. However there was an imbalance between the groups for availability of samples for re-examination, in favour of the observation-only arm.

Prayer-Galetti et al (2000): Disease free survival in patients with pathological ‘C stage’ prostate cancer at radical retropubic prostatectomy submitted to adjuvant hormonal treatment
In this prospective randomised controlled study, patients with locally advanced prostate cancer undergoing RP were randomised 1:1 to goserelin acetate 3.6 mg monthly, or no adjuvant treatment. The endpoints were tumour progression and ‘specific survival’. 201 patients were enrolled 1991-1994. 38% had seminal vesicle invasion and 17% bladder neck involvement. The authors report a 25.2% advantage in disease-free survival for the AHT group, which was statistically significant. The authors also state that the advantage is less relevant for the sub-group with Gleason 8-10.

Assessor’s comment:
There appears to be a clinically relevant benefit for adjuvant GnRH analogue treatment to radical prostatectomy in locally advanced prostate cancer. However, a detailed assessment is not possible as the literature report is brief.

Siddiqui et al 2010: Impact of adjuvant androgen deprivation therapy after radical prostatectomy on the survival of patients with pathological T3b prostate cancer
Design
This was a retrospective case-control study, using the Mayo Clinic Prostatectomy Registry. Patients undergoing radical prostatectomy who had received ADT were matched 1:1 to controls (undergoing radical prostatectomy for stage T3b prostate cancer, no ADT) using clinical and pathological variables (margin status, Gleason score, preoperative PSA, age, year of surgery).

Study population
12,115 patients who underwent RP between 1987 and 2002 were reviewed to identify patients with stage T3bN0 prostate cancer who received adjuvant ADT (n=191). Patients receiving neoadjuvant treatment or having lymph node involvement were excluded.

Treatments
These included GnRH analogues, anti-androgens or orchidectomy, within 90 days of radical prostatectomy. 91 patients received LHRH agonists only.

Results
At 10 years, patients who received adjuvant ADT after RP experienced improved biochemical PFS (60% vs 16%, p<0.001), local recurrence-free survival LRFS (87% vs 76%, p=0.002), systemic PFS (91% vs 78%, p=0.004) and cancer-specific survival (94% vs 87%, p=0.037). Overall survival at 10 years was similar in both groups (75% vs. 69%,
p=0.12). After adjusting for matching factors using a stratified Cox model, outcomes were similar except for a loss of statistical significance for prostate cancer death.

If only patients taking GnRH analogues are considered, a statistically significant benefit remains for PSA progression and clinical local recurrence. Although orchidectomy appears to confer a survival benefit over LHRH agonists, a difference is also observed between the respective matched controls.

**Assessor's comment:**
This study, although retrospective case-control in design, provides some support for the use of immediate long-term adjuvant treatment, including GnRH analogues, in patients undergoing radical prostatectomy for locally advanced disease who are at high risk of disease progression.

Wong et al 2009: Role of androgen deprivation therapy for node-positive prostate cancer

**Design**
This was a retrospective observational cohort study using Medicare (SEER) data to assess the benefit of adjuvant ADT following radical prostatectomy for node-positive prostate cancer. Outcomes for patients receiving ADT were compared to those for patients not receiving ADT. Propensity scores were used to balance potential confounders. Cox proportional hazards method was used to measure the impact of adjuvant ADT on overall survival.

**Study population**
The authors constructed a cohort of men who underwent radical prostatectomy 1991-1999, and who were found to have positive regional lymph nodes. Of 731 men identified, 188 received adjuvant ADT. The median age in both groups was 70 years.

**Treatment**
Men were classified as receiving adjuvant ADT if this was administered within 120 days of radical prostatectomy.

**Results**
After adjustment of the propensity score, there was no statistically significant difference in overall survival (HR 0.95; 95% CI 0.71 to 1.27) or prostate cancer specific survival. Altering the definition of adjuvant treatment did not affect the results.

**Assessor’s comment:**
This retrospective cohort study provides some evidence of a lack of benefit of adjuvant ADT following radical prostatectomy. The population could be considered locally advanced.

Moul et al 2004: Early versus delayed hormonal therapy for PSA-only recurrence of prostate cancer after radical prostatectomy.

**Design**
This retrospective observational cohort study examined clinical outcomes in men undergoing primary radical prostatectomy who developed PSA-only recurrence, comparing early vs. delayed hormone therapy. Patients were stratified by Gleason score, PSA doubling time and timing of recurrence. Cox proportional hazards models were used to evaluate the effect of early and late hormone treatment on clinical outcome.
Study population and treatment
1352 men with PSA-only recurrence (PSA after surgery > 0.2 ng/mL) were divided into 2 groups: early hormone therapy group (n=355) who received treatment after PSA recurrence but before clinical metastasis, and late hormone treatment group (n=97) who received no hormone treatment before clinical metastasis by current follow-up.

Endpoints
The primary endpoint was development of clinical metastases.

Results
Early hormone treatment was associated with delayed clinical metastasis in higher risk patients (eg Gleason > 7, PSA doubling time of ≤ 12 months). However, overall, there was no association between early vs. delayed treatment and development of metastasis.

Assessor’s comment:
This paper is less relevant to the proposed new indication which is for adjuvant hormone therapy, rather than therapy after biochemical recurrence. However, it provides some evidence that higher risk patients may benefit from earlier hormonal treatment.

Cheng et al 2001: Risk of prostate carcinoma death in patients with lymph node metastasis
Design
This was an observational cohort study.

Study population and treatments
The authors reviewed 3463 consecutive Mayo clinic patients who underwent radical prostatectomy and bilateral pelvic lymphadenectomy for prostate cancer 1987-1993. 322 had lymph node metastasis at time of surgery, and of these, 297 also received adjuvant hormone treatment within 90 days of surgery.

Endpoints
PFS and cancer-specific survival were use as endpoints in univariate and multivariate Cox proportional hazards models. Median follow-up was 6.3 years.

Results
The authors observed that patients with regional lymph node metastases who underwent radical prostatectomy and received adjuvant hormone treatment achieved ‘excellent local disease control’. However a direct comparison of outcomes between those receiving adjuvant treatment, and those not receiving adjuvant treatment was not presented.

Assessor’s comment:
This observational cohort study was not specifically designed to investigate the association between use of adjuvant treatment after radical prostatectomy, and clinically important outcomes. Instead, patients with and without positive lymph nodes were compared. Therefore, conclusions of relevance to the proposed indication cannot be drawn.

Dorff et al 2011: Adjuvant androgen deprivation for high-risk prostate cancer after radical prostatectomy: SWOG S9921 study
The authors report the results in the ADT-alone control arm of a randomised controlled trial of ADT alone or in combination with mitoxantrone chemotherapy in patients with high risk prostate cancer undergoing radical prostatectomy. 481 men with extraprostatic extension or high Gleason score received ADT alone (goserelin and bicalutamide for 2 years). After a median follow-up of 4.4 years, the estimated 5-year biochemical failure-free survival is 92.5% (95% CI: 90-95) and 5-years overall survival is 95.9% (95% CI: 93.9-97.9).

Assessor's comment:
For the purposes of this assessment, this study is essentially a single arm prospective study of high risk patients undergoing radical prostatectomy. 53% were Gleason 8-10, 77% were at least stage T3. 66% had a positive surgical margin. Median age was 60.7. Therefore although high risk, these patients were younger than most cohorts referred to by the MAH, perhaps due to the possibility of randomisation to chemotherapy. The authors also state that only men with normal cardiac function were included. This study does not address question of whether immediate ADT after RP is superior to starting ADT at time of biochemical or clinical recurrence.

Treatment guidelines
The MAH refers to three treatment guidelines in support of an indication in neoadjuvant treatment prior to radiotherapy:

- European Association of Urology Guidelines on Prostate Cancer 2012 (Heidenreich et al 2012)

NICE Clinical Guideline CG58: Prostate cancer: diagnosis and treatment (February 2008)
The guideline recommends radical radiotherapy or radical prostatectomy as preferred treatments in patients with high-risk localised disease and locally advanced disease. If radical radiotherapy is used as primary treatment in locally advanced disease, then neoadjuvant hormone therapy is recommended, in addition to adjuvant hormone treatment for up to 3 years. The guideline also states that high risk localised disease can be considered under the heading ‘locally-advanced’.

The guideline explicitly states that adjuvant hormone treatment in addition to radical prostatectomy is not recommended, even in men with margin-positive disease, other than in the context of a clinical trial.

EAU Guideline (Guidelines on prostate cancer; European Association of Urology 2012)
The definitions used for high risk localised and locally advanced disease are consistent with the NICE guideline.

The guideline recommends androgen deprivation therapy prior to and during radiotherapy, for high risk patients.

The guideline states that there is no benefit for survival in using adjuvant hormone treatment with radical prostatectomy in patients with locally advanced disease. However
Adjuvant hormone treatment is an option after radical prostatectomy for locally advanced disease if more than 2 positive nodes are identified.

**NCCN Guidelines version 3.2012: Prostate cancer**
This guideline recommends the following treatment options:

*High risk clinically localised (include T3a, as well as Gleason 8-10, PSA >20)*
- radiotherapy + long-term neoadjuvant/concomitant/adjuvant ADT (2-3 years)
- radical prostatectomy + pelvic node dissection

*Locally advanced T3b-T4*
- radiotherapy + long-term neoadjuvant/concomitant/adjuvant ADT (2-3 years)
- radical prostatectomy + pelvic node dissection

**Assessor’s comment:**

Other relevant guidelines include
- MDT (Multi-disciplinary Team) guidance for managing prostate cancer. Second edition (November 2009) produced by British Uro-Oncology Group (BUG), the British Association of Urological Surgeons (BAUS) Section of Oncology and the British Prostate Group.
- European Society for Medical Oncology (ESMO)

**MDT guidance** (supported by an educational grant from Ferring Pharmaceuticals, Novartis and Sanofi-Aventis)
This guideline groups high risk localised disease with locally-advanced disease for the purposes of treatment recommendations. Neo-adjuvant hormone therapy is provided as an option in conjunction with external beam radiotherapy. Radical prostatectomy is not presented as a primary treatment option in high-risk localised or locally-advanced disease.

**ESMO guidance**
The guideline recommends radical prostatectomy, or radiotherapy + (neo)adjuvant treatment, in high-risk localised or locally advanced group. Adjuvant hormone therapy after radical prostatectomy is not recommended.

**Evaluation**

*As neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.*
The submitted literature references support the use of GnRH analogues as neoadjuvant treatment prior to radiotherapy in both the high-risk localised and locally advanced populations. Benefit is demonstrated for overall survival, as well as clinically relevant disease-specific endpoints. However, in the majority of studies, the GnRH analogue used is goserelin. There are no long-term studies of triptorelin as neoadjuvant treatment prior to radiotherapy. Out of the GnRH analogue class, only goserelin is currently approved in the UK for the neoadjuvant indication, as follows:

*As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer where Zoladex has demonstrated improved disease-free survival (see section 5.1)*
The MAH has submitted literature data from two single-arm studies in which triptorelin was used as neoadjuvant treatment prior to radiotherapy. Both studies demonstrate a statistically significant reduction in prostate volume, measured just prior to radiotherapy, compared to pre-biopsy. Ozyigit et al also demonstrated a statistically significant reduction in PSA level just prior to radiotherapy, compared to pre-biopsy. The reduction in prostate volume is considered clinically relevant, as there is a consequent reduction in planning volume. As a result, an increased radiation dose can be delivered to the affected tissues, without increasing damage to surrounding normal tissue.

Clinical guidelines support the use of GnRH analogues as neoadjuvant treatment prior to radiotherapy in patients with localised and locally advanced prostate cancer. The guidelines do not differentiate between GnRH analogues.

For the indication to be approvable, it is necessary to extrapolate the results of long-term randomised controlled studies of GnRH analogues other than triptorelin. It is widely accepted that the efficacy of GnRH analogues in prostate cancer depends on the reduction of testosterone to castrate levels (0.5 ng/mL). It is has been demonstrated in previous applications that castrate levels are achieved during triptorelin treatment. Therefore the results from studies of other GnRH analogues can be used in support of the proposed indication.

**Conclusion**

The submitted evidence supports the use of triptorelin as neoadjuvant treatment prior to radiotherapy in patients with high-risk localised and locally advanced prostate cancer. The proposed indication is approvable.

**As adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.**

There is a lack of data to support the benefit of GnRH analogues as adjuvant treatment to radical prostatectomy in this population. The data from Messing et al, using goserelin, appear to demonstrate a clear survival advantage in patients with locally-advanced disease found to have nodal disease following radical prostatectomy. However this study was planned in the pre-PSA era, so that intervention in the control arm was based on clinical rather than biochemical progression. The consensus from guidelines is that adjuvant GnRH analogues are not recommended following radical prostatectomy.

Zoladex (goserelin) is approved in the UK for the following indication:

*As adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression where Zoladex has demonstrated improved disease-free survival (see section 5.1)*

Prostap (leuprorelin) is also approved for the adjuvant indication, with identical wording to that proposed for triptorelin. There is also wording in section 5.1 of the Prostap SmPCs, identical to that proposed for triptorelin, reflecting the lack of clinical data for leuprorelin in the adjuvant indication.

There is no available clinical data for triptorelin as adjuvant treatment after radical prostatectomy. As discussed for the neoadjuvant radiotherapy indication above, results of studies using other GnRH analogues can be extrapolated, in support of the proposed indication.
Conclusion
The submitted evidence is supportive of the use of triptorelin as adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression. The proposed indication is approvable.

The SmPC has been suitably updated to reflect the proposed changes.

Decision – Granted 02/05/2013
Annex 3

VARIATION ASSESSMENT REPORT

Our Reference: PL 34926/0002 - 0023
Product: Decapeptyl SR 22.5mg powder and solvent for suspension for injection
Marketing Authorisation Holder: Ipsen Limited
Active Ingredient: Triptorelin

Reason

To update section 4.2 (posology and administration) of the SmPC in order to reflect recent evolutions in the prostate cancer therapeutic armamentarium and current medical practice, in accordance with official international and European treatment guidelines. To also update section 4.8 (undesirable effects) of the SmPC to include the Yellow Card adverse reactions reporting scheme text.

Introduction

Decapeptyl (triptorelin) is authorised for the treatment of prostate cancer. It is a gonadotrophin releasing hormone (GnRH) agonist analogue which provides androgen suppression, or ‘medical castration’. Some treated patients will eventually develop castrate resistant prostate cancer (CRPC), defined as disease progression in the presence of testosterone levels < 50 ng/dL.

The MAH proposes changes to sections 4.2 and 4.8 of the SmPC, as discussed below.

No changes to the package leaflet or labelling are proposed.

Supporting Evidence

The MAH has submitted a clinical overview with references, to support the proposed changes. The overview is signed by a medically qualified expert. No new clinical data are submitted.

Proposed change to Section 4.2

In patients treated with GnRH analogues for metastatic prostate cancer, treatment is usually continued upon development of castrate-resistant prostate cancer. Reference should be made to relevant guidelines.

Reference is made to current treatment guidelines providing recommendations for patients with CRPC.

The European Association of Urology (2013) guidelines on prostate cancer states: ‘Continued testicular androgen suppression in CRPC has a minimal overall effect. The recommendation to continue ADT with LHRH analogues, despite PSA progression, is based on the data of Manni et al. They demonstrated significantly lower survival rates in patients without complete androgen blockade (CAB). However, these data have been
challenged by two trials that showed only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies. However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. Androgen suppression should therefore be continued indefinitely in these patients.’

The National Comprehensive Cancer Network (NCCN) guideline on prostate cancer states: ‘androgen receptor activation and autocrine/paracrine androgen synthesis are potential mechanisms of recurrence of prostate cancer during ADT (castration-recurrent prostate cancer [CRPC]). Thus, castrate levels of testosterone should be maintained while additional therapies are applied.’

The MAH also makes reference to the EPAR and SmPC for Zytiga 250 mg tablets (abiraterone). Zytiga is indicated with prednisone or prednisolone for:
- the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated
- the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

Section 4.2 of the Zytiga SmPC states:
‘Medical castration with LHRH analogue should be continued during treatment in patients not surgically castrated.’

The MAH justifies the proposed change as reflecting recent evolutions in the prostate cancer armamentarium and current medical practice. In addition, reference is made to the SmPC guideline requiring reference to official recommendations, and giving information on the normal duration of use.

Proposed change to Section 4.8

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

The wording is included to be in line with the latest CMD(h) QRD template.

Evaluation

Proposed change to Section 4.2

In patients treated with GnRH analogues for metastatic prostate cancer, treatment is usually continued upon development of castrate-resistant prostate cancer. Reference should be made to relevant guidelines.

The referenced treatment guidelines recommend that patients with CRPC should remain on androgen suppression therapy, unless surgically castrated. Other guidelines likely to be referred to by UK medical practitioners also recommend this approach:
• NICE prostate cancer guideline 2008 (CG58):
  ‘Even when the disease becomes hormone refractory the androgen receptor on the
cancer cells can remain active and LHRHa therapy is usually continued.’
• ESMO clinical practice guidelines 2013:
  ‘Patients who develop CRPC should continue androgen suppression and be
considered for further hormonal therapies; chemotherapy might be preferable in those
with poor initial hormone response or severe symptoms.’

The SmPC guideline dated September 2009 makes the following recommendation for
Section 4.2, of relevance for this variation application:
‘Where appropriate, a reference to official recommendations should be made.’
‘Where appropriate, the following points should be addressed:
[…..]
  • the normal duration of use and any restrictions on duration and, if relevant, the
  need for tapering off, or advice on discontinuation
[…..]’

It is agreed that advice to continue GnRH analogue treatment in CRPC patients is in line
with current treatment guidelines. It is also agreed that the inclusion of such advice is in
line with the SmPC guideline, and might be useful to prescribers.

**Proposed change to Section 4.8**

The proposed additional text regarding the reporting of suspected adverse events is in line
with the latest CMD(h) annotated QRD template for MR/DC procedures (April 2013).
The text is therefore acceptable.

**Conclusion**

The proposed wording in Section 4.2 is considered sufficient to inform prescribers. The
inclusion of standard wording in Section 4.8, regarding reporting of suspected adverse
reactions, is also endorsed.

**The SmPC has been suitably updated to reflect the proposed changes.**

**Decision – Granted 01/05/2013**